



# 100+ Clinical Cases in Pediatrics

**5**<sup>th</sup> Edition

**R Arvind**



**100+**

# **Clinical Cases in PEDIATRICS**





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# **Clinical Cases in PEDIATRICS**

**Fifth Edition**

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### 100+ Clinical Cases in Pediatrics

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**Dedicated to**

*My Beloved Father*  
*Late Shri N Rajasekhar*



# PREFACE TO THE FIFTH EDITION

*100+ Clinical Cases in Pediatrics, 5th edition* has been thoroughly revised and elaborated. All the possible suggestions, kind remarks from the students and readers have been taken into consideration in this edition. All the cases have been completely updated. Discussion, diagnosis and management of each case have been revised. Three new cases Henoch-Schönlein purpura, Infectious mononucleosis and Obesity have been added in this edition.



Clinical features of the cases have been illustrated with line diagrams and photographs. A comprehensive glossary has been completely revised, elaborated and updated. This helps as a ready reckoner for undergraduate and postgraduate students preparing for various competitive examinations.

This book attempts to improve the clinical and practical approach for undergraduate medical students, interns, and residents in presentation and diagnosis of clinical cases. It will be helpful for the postgraduate students and practicing pediatricians.

**R Arvind**



# PREFACE TO THE FIRST EDITION

With the new Medical Council of India (MCI) guidelines laying more emphasis on clinical and practical skill development rather than theoretical knowledge, there is immense need for a book on common clinical cases in pediatrics. The present book attempts to fulfill this need and aims to help the undergraduate medical students, interns, and residents in diagnosis and presentation of clinical cases. It would also be helpful to the postgraduate students and the practicing pediatricians.

The most commonly encountered and typical cases have been grouped into 12 categories that include birth defects and genetic disorders, respiratory, cardiovascular, gastrointestinal, hematological, renal, central nervous system, endocrine and metabolic, nutritional, oncological disorders, disorders of connective tissue, bones and joints, and the infectious diseases. Each case has been discussed in detail under history, clinical features, differential diagnosis, complications, and treatment. At the end of each case, multiple choice questions have been added to help the student in revision. A comprehensive and exhaustive glossary has also been included. The book is well illustrated with photographs wherever required.

I thank my wife Dr Chetana, for her suggestions and professional help. I am also thankful to Rachana and Shikhar, the gems of my family, for their cooperation.

I express my deep gratitude to M/s Cyber Avenue, for typing the manuscript.

**R Arvind**



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# Down Syndrome

## PRESENTING COMPLAINTS

An 8-month-old girl brought with the complaint of delayed developmental milestones since 6 months.

## History of Presenting Complaints

An 8-month-old girl was brought to the hospital with the history of delayed developmental milestones. The mother was concerned that her child did not even develop neck control. She observed that her child was flabby and did not turn from side-to-side while lying on the bed.

## Past History of the Patient

Child was born at term after a normal pregnancy. She was the first sibling of nonconsanguineous

marriage. Maternal age at the time of the delivery of this child was 35 years and the age of the father was 38 years. Baby cried immediately after the delivery.

The birth weight was 3.25 kg, the head circumference was 35 cm and the length of the child was 49 cm. There was normal physiological jaundice after the delivery. Breast milk was given at birth and was on exclusively on breast milk till 6 months. There were no feeding problems. Child had social smile at the age of 3 months. She did not develop neck control even at the age of 8 months for which she had been brought to the hospital. She had been completely vaccinated.

## EXAMINATION

Child appeared small for her age. She was playing on the examination table. Her height and weight were on 3rd centile for her age and her head circumference was just below 3rd centile.

She was afebrile, pulse was 116 per minute, respiratory rate was 26 per minute. Blood pressure recorded was 60/40 mm Hg. There was no pallor, no lymphadenopathy and no edema.

Her face was round, there was upward slanting of the eyes with marked epicanthic fold. The nose was small with depressed nasal bridge. The hands were broad and small with short fingers. The little finger was incurved. There was a single palmar crease, i.e., simian crease. Neurological examination revealed the presence of generalized hypotonia. Cardiovascular system revealed the presence of the pansystolic murmur. Per abdominal examination was normal.

## INVESTIGATION

Hemoglobin	: 13 g/dL
TLC	: 7,800 cells/cu mm
DLC	: $P_{65} L_{30} E_3 M_2$
Chromosome analysis	: Showed three copies of chromosome 21
X-ray chest	: Normal

### CASE AT A GLANCE

#### Basic Findings

Weight	: 6.5 kg (3rd centile)
Head circumference	: 40 cm (2nd centile)
Temperature	: 37°C
Pulse rate	: 116 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 60/40 mm Hg

#### Positive Findings

##### History

- Delayed developmental milestones
- Increased maternal age
- Increased paternal age

##### Examination

- Upward slanting of eyes
- Epicanthic folds
- Small nose
- Flat nasal bridge
- Broad hands
- Incurving of the little finger
- Simian crease
- Pansystolic murmur

##### Investigation

- Chromosome analysis revealed three copies of chromosome 21
- Chest radiograph showed right ventricular hypertrophy

## DISCUSSION

A child with generalized hypotonia, delayed developmental milestones, upward slanting of the eyes, flat nasal bridge, simian crease with incurving of the little finger suggests the Down syndrome. The diagnosis is supported by history advanced age of the parents.

John Langdon Down first described the phenotype of the syndrome in 1866. Hence, this was named after him as Down syndrome. It was determined that it was caused by extra chromosome 21 only in 1959.

It is the most common chromosomal disorder. The incidence (without antenatal screening) is 1 in 650 live births. It is the most common autosomal trisomy and the cause of severe learning disorder. In trisomies there are three representatives of particular chromosome. In Down syndrome, the chromosome number 21 is represented in triplicate.

### Cytogenetics

In 90% of cases, Down syndrome is associated with “regular” 21 trisomy giving a total number of 47 chromosomes. The other 10% are due to the balanced translocation involving chromosome 21. Part of an extra chromosome is attached to another. The another extra chromosome is usually 13, 14, 15, 21 or 22.

The origin of the extra chromosome is either from mother or from the father. In most cases this is from the mother. This is common in a child of the mother conceiving at older age. This is attributed to the exposure of the maternal oocyte to the harmful environmental influences for a longer period. This is because of graafian follicle present in the fetal life which exists throughout the female reproductive life. Over ripening of the ovum results from either delayed fertilization or decreased frequency of the coitus. Viral hepatitis is incorporated because of virus-induced disturbance of chromosomal segregation.

Maternal age-related chromosomal abnormalities include all trisomies and some sex chromosomal abnormalities except 45X and 47XYY.

The extra chromosome 21 may result from meiotic nondisjunction, translocation and mosaicism.

- *Meiotic nondisjunction (94%)*: The majority are due to errors in maternal meiosis, which increase with maternal age. Here most cases result from error at meiosis. Here the pair of chromosome 21s fails to separate. Hence, one gamete has two chromosome 21s and other

one has none. The fertilization of the gamete with the two chromosome 21s results with zygote trisomy 21. Meiotic nondisjunction increases with increasing maternal age. As the proportion of pregnancies in elder mother is less most affected newborn compared to young mothers. Meiotic nondisjunction can occur in spermatogenesis, hence extra 21 can be paternal origin also. But 5% are paternal derived.

- *Translocation (5%)*: Here, the chromosome 21 is translocated on to a chromosome 14 and more rarely on chromosomes 13, 14, 15, 21 or 22. This is known as Robertsonian translocation. In about 95% there are three standing copies of chromosome 21 with set of 46 chromosomes. In some cases, i.e., phenotypically normal carrier there is balanced translocation appearing to have only 45 chromosomes, but one chromosome 21 is joined to another chromosome.
- *Mosaicism (1%)*: Here some cells are normal and some have trisomy 21. This usually arises after the formation of zygote by nondisjunction mitosis. The phenotype may be milder in Down syndrome mosaicism.

## CLINICAL FEATURES (FIGS. 1A TO E)

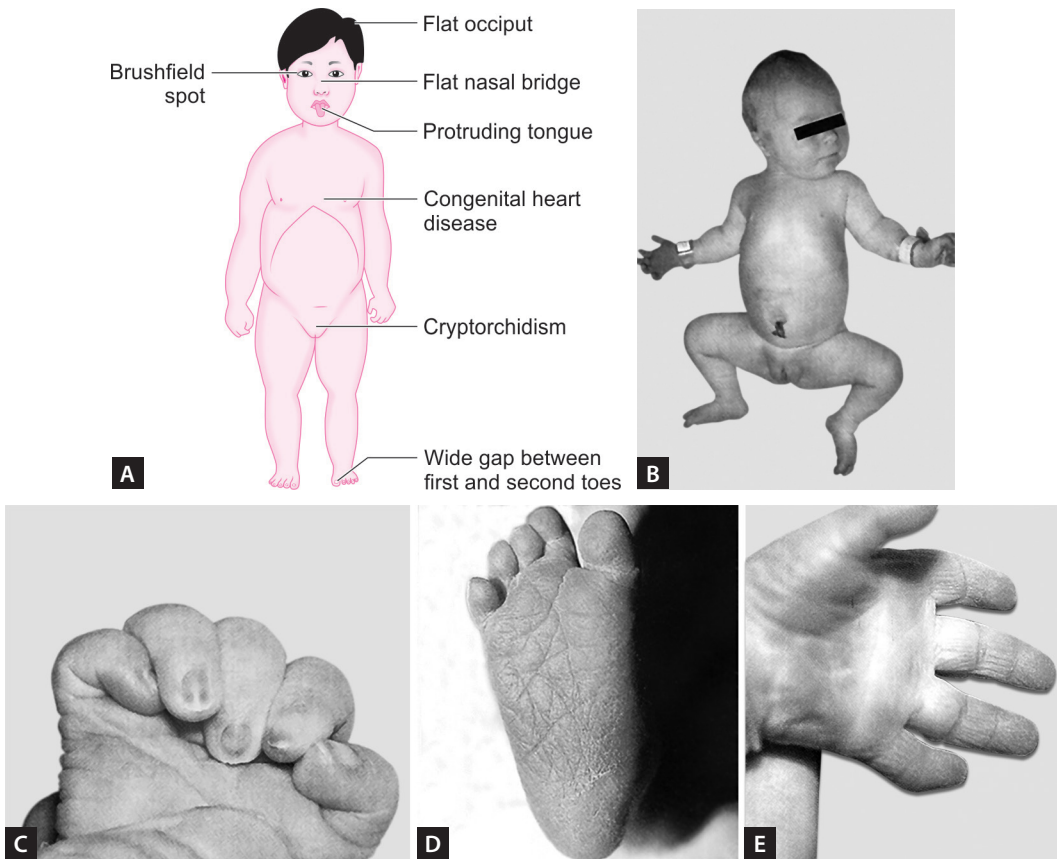
Down syndrome is usually suspected at birth because of baby's facial appearance, but is very difficult to diagnose depending on physical features. Affected infants are usually hypotonic and other clinical features are listed below. But it has to be confirmed by karyotyping. Diagnosis of Down syndrome in preterm baby is more difficult than in term baby.

### GENERAL FEATURES

- Mental retardation
- Hypotonia
- Imperforate anus
- Hirschsprung's disease
- Leukemia
- High-arched palate

### Diagnostic Features of Down Syndrome at Birth

- Mongoloid face
- Poor Moro reflex
- Hypotonia
- Hyperflexible joints
- Excessive skin on neck
- Slanted palpable fissure
- Pelvic dysplasia



**Figs. 1A to E:** (A) Clinical features; (B) Down syndrome; (C) Single palmar crease; (D) Sandal gap between big and second toe; (E) Single palmar crease.

- Anomalous auricles
- Dysplastic mid phalanx of fifth finger
- Single palmar crease
- Flat occiput
- Wide sandal gap between big and second toe

Flat facies, epicanthic fold (a fold of skin running across the inner edge of palpebral fissure) and upward slanting of the eyes are present. Nose is small with flat nasal bridge. Furrowed protruding tongue is present. The head is brachycephalic, the palpebral fissures obliqued, inwards and downwards towards the broad flat nose.

The eyelids show signs of chronic blepharitis, the ears are large, and lips are fissured with protruded tongue. The almond-shaped eyes, the presence of epicanthus, the florid complexion and absence of fatty masses help to distinguish Down syndrome from cretinism.

A variety of congenital and acquired medical problems are associated with the Down syndrome. These are best categorized according to the

chronological age. Screening of asymptomatic individuals at regular interval is strongly recommended.

- *Congenital heart disease* occurs in 40%. These are responsible for the morbidity and mortality during the first 2 years of life. All children should be evaluated before 9 months of age including echocardiography. The most common cardiac lesions are endocardial cushion defects accounts 40%. Other lesions include atrioventricular (AV) canal, isolated ventricular septal defect (VSD), atrial septal defect (ASD) or patent ductus arteriosus (PDA) and tetralogy of Fallot.
- *Gastrointestinal tract anomalies* are seen in 6–12% of Down syndrome. These include duodenal stenosis or atresia, imperforate anus, Hirschsprung's disease, tracheoesophageal fistula, esophageal atresia, bile duct atresia, malrotation and pyloric stenosis. Physiological complications include oral motor dysfunction or gastroesophageal reflux.



- *Respiratory problems* include recurrent otitis media, sinusitis, rhinitis, bronchiolitis, and pneumonia. These carry high mortality if associated with uncorrected heart disease. These tend to become less common with the age and growth of the craniofacial and respiratory structures.
- *Ophthalmic problems* include Brushfield spots (**Fig. 2**) are white-speckled areas that occur in the periphery of iris. These are seen in 75% of patients with Down syndrome. It is also present in 7% of normal newborn. Congenital cataract is seen in about 1–2% of patients.
- *Thyroid problems* include increased risk of congenital hypothyroidism due to the absence or aplasia of thyroid gland which occur in 1–2% of newborn. Acquired hypothyroidism is seen in 2–7% of children. The risk of Graves disease is also increased in individuals with Down syndrome. Thyroid function tests (T3, T4 and TSH) are recommended once in neonatal period and then every year.
- *Transient myeloproliferative disorder (TMD)* is seen in the first few months of life. There will be elevated peripheral blood leucocyte count with predominant blast forms. This will confuse the diagnosis of true congenital leukemia. Newborns of TMD are increased risk for developing nonlymphocytic leukemia before the age of 5 years. Patients with Down syndrome are increased risk of lymphoproliferative disorders, including acute lymphoblastic leukemia, acute myeloid leukemia, myelodysplasia, and transient lymphoproliferative syndrome.
- *Hearing defects* of incidence of transient conductive hearing loss is due to otitis media, middle ear effusion or impacted cerumen.



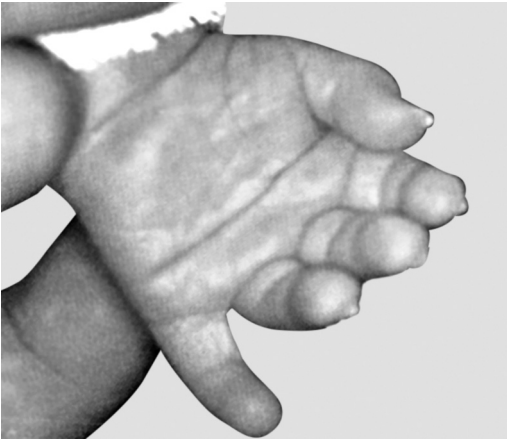
**Fig. 2:** Brushfield spots.  
(For color version see Plate 1)

These are more prone to serous otitis media during first year of life. Routine evaluation before 6 months of age and then every year is advised. Sensorineural or mixed hearing loss may be seen.

- *Central nervous system problems* include neuromotor dysfunction is characterized by generalized hypotonia with diminished primitive and deep tendon reflex. Brain size is often normal throughout gestation and first 6 months of life. Deceleration occurs during the second half of first year. There is dysgenesis of the cerebral cortex and cerebellum. There is delay in myelination during the first year of life. This may be the primary neurological substrate of neuromuscular dysfunction. Seizures especially infantile spasms may occur. There is delay in prelinguistic visual perception and visual motor milestones are present by the end of the first year.

Dysplasia of the brain is best reflected by changes in the brain growth and head circumference in the first few years of life. There is generalized hypocellularity of the brain. There is reduction in neuronal numbers and density. Decreased myelination is noted in cerebral hemisphere, basal ganglia, cerebellum and brain stem during the first few years of life. There will be greater deficits in verbal linguistic skills relative to visual spatial skill.

- *Obstructive sleep apnea (OSA)* is seen in more than 30% of Down syndrome. The symptoms include snoring, restless sleep, unusual sleep position excessive mouth breathing, daytime somnolence or behavioral changes. Predisposing factors include small oral cavity, relative macroglossia, narrowing of the upper air way, hypotonia of the pharyngeal muscles, chronic rhinitis, enlarged tonsils or adenoids.
- *Intellectual disability* in children with Down syndrome is variable usually mild to moderate. Development usually progresses steadily at a slower pace, with no evidence of regression. Children learn to walk and develop communication skills and often function more effectively in social situations then would be predicted on the basis cognitive assessment alone. Early intervention, proper medical management, and educational and vocational training can significant affect the level of functioning in children and adolescents with Down syndrome and facilitate their transition into adulthood.



**Fig. 3:** Simian crease.

- **Psychiatric disorders** such as disruptive disorders include attention-deficit hyperactivity disorder (ADHD), conduct/oppositional and aggression. Repetitive disorders or autistic spectrum disorders are seen. The medical conditions responsible for behavioral problems include hearing loss, OSA and medications. Stereotypic or repetitive behavior include rocking, hand flapping, staring at fingers or lights, and shaking objects.
- **Simian crease (Fig. 3):** A single palmar crease is present in 45% of Down syndrome. Hypoplasia of the middle phalanx in the fifth finger is present. This produces clinodactyly, i.e., deflection of the finger. Hands are short and broad. Gap between first and second toe is wide, i.e., wide sandal gap.
- **Subluxation of joints:** These children are susceptible to the subluxation of hips, patella and cervical spine. About 10–30% atlanto-occipital subluxations occur in cervical spine.

#### ESSENTIAL DIAGNOSTIC POINTS

- Mental retardation
- Small, brachycephalic head
- Mongoloid facies—upslanting palpebral fissures, epicanthic folds, midface hypoplasia, and small, dysplastic pinnae
- Congenital heart defects
- Anomalies of gastrointestinal (GI) tract
- Generalized hypotonia
- Leukemia

#### Typical Craniofacial Appearance

- Round face, flat nasal bridge
- Epicanthic fold
- Brushfield spots

- Upslanting palpebral fissures
- Small mouth
- Small ears
- Flat occiput

#### DIAGNOSIS

The following are the indications for the antenatal diagnosis:

- Advanced maternal age
  - H/o child with Down syndrome
  - Translocation carrier
  - Partners of translocation carriers
- The tests can be *fetal* and *maternal*.

#### Fetal Tests

##### *Fetal Umbilical Blood Sampling*

This is done at 18–20 weeks of gestation. Fetal blood cells are subjected to chromosomal culture. The results will be available within a week.

##### *Fetal Cells in the Maternal Circulation*

Fetal cells are found in maternal circulation in the first trimester. These cells are used for chromosomal analysis using polymerase chain reaction (PCR) technique.

#### Maternal Tests

Maternal antenatal test can be divided into screening and diagnostic tests.

##### *Screening Tests*

All pregnant should undergo screening tests measuring biochemical markers in blood samples.

- **Ultrasound:** Ultrasound is the commonly used screening test to detect the structural fetal anomalies. In Down syndrome it can be divided into first trimester and second trimester scanning.
  - **First trimester scanning** is best done at 11 weeks of gestation. Here the nuchal soft tissue fold is measured. It is the space between the back of the fetal neck and overlying skin. Increased thickness, i.e., >4 mm is called nuchal translucency. It is associated with aneuploidy, i.e., Down syndrome.
  - **Second trimester ultrasound** indicates associated markers of Down syndrome. These markers can be major or minor markers. Major markers include cardiac anomalies such as endocardial cushion defects, neural tube defects, cystic hygroma

and omphalocele. Minor markers have lower association with aneuploidy. These include nuchal translucency, short femur, short middle phalanx of fifth digit, echogenic intracardiac foci, pyelectasis, hypoechogenic bowel, mild ventriculomegaly and choroids plexus cysts.

- **Serum screening:** Here biochemical analytics are measured in maternal blood sample. Serum screening is well established at second trimester. Here the combination of increased human chorionic gonadotropin (hCG), decreased  $\alpha$ -fetoprotein, decreased unconjugated estriol and increased inhibin are used. If three or four biochemical analytics are detected, it is called as triple/quadruple test, respectively.

### Diagnostic Tests

There are two diagnostic tests, i.e., amniocentesis and chorionic villus sampling. Prenatal fetal karyotype with these tests is advised.

- **Amniocentesis:** It is best done between 10 and 12 weeks by transcervical or transabdominal route, and hence diagnosis can be done in first trimester. It can be done at 16 weeks of gestation. Amniotic fluid is withdrawn with the ultrasound guidance. The amniotic fluid cells are derived from epiblast. They reflect the true constituents of embryo. These cells are cultured and cytogenetic analysis is done. The risk of miscarriage is 1:200.
- **Chorionic villus sampling (CVS):** It is best done at or beyond 10 weeks of gestation. If it is done prior to 10 weeks it is associated with limb anomalies. It has about 1:100 risk of miscarriage. Transabdominal CVS and cordocentesis are considered at 16–18 weeks.

With the ultrasound guidance, the chorionic villi are removed via abdominal or less commonly via vaginal route. The cells of CVS arise from trophoblast or villus core cells. These reflect more with embryonic cells. These cells are cultured and cytogenetic analysis is done. The advantage over amniocentesis is that it is done earlier in gestation and that if trisomy 21 is detected, then a surgical termination can be done.

- **Karyotype:**
  - It refers to the systemic arrangement of previously stained and banded chromosomes of single cell by pairs. It is performed on blood lymphocytes or skin fibroblast. The cells are cultured and

arrested in mitoses during metaphase. Then it is fixed and stained.

- Karyotype is mandatory to confirm the diagnosis. It is must before the diagnosis is conveyed to the parents. It is helpful for genetic counseling as it is critical to distinguish complete trisomy 21, from trisomy 21/mosaicism or unbalanced translocation.
- If there is free trisomy 21, parental chromosome need not be examined. If the baby has translocation, the parental chromosomal analysis is recommended, since one of the parents may well carry the translocation in balanced form (25% of cases). If one carries balanced translocation, other relatives should be counseled.

### Radiological Findings

- Eleven ribs
- 2–3 ossification centers of manubrium
- Hypoplasia of the base of the skull, facial bones and middle phalanx of fifth finger
- Accessory epiphyses at base of second metacarpal
- Coxa valga
- Bony pelvis, and iliac are broad and flared, acetabular and iliac angles are reduced.

### Dermatoglyphic Findings

- Distal palmar triradius, or large angle hypothermia pattern distal loop in third interdigital area
- Predominance of ulnar loops on the digits and radial loops or on the 4th and 5th fingers
- Hallucal area tibial pattern in the feet
- Marked crease between great and second toes

### Recurrent Risk

One child with trisomy 21 due to nondisjunction, the risk of recurrence 1 in 200 for mothers under age of 35 years. The risk of recurrence is 10–15%, if the mother is the translocation carrier and is 2.5% if the father is carrier. If the parent carries rare 21:21 translocation, all the offsprings will have Down syndrome. If neither parent carries translocation (75% of the cases) risk of recurrence is less than 1%.

Carrier mother may produce three types of viable offspring:

1. Normal phenotype and karyotype
2. Phenotypically translocation carrier
3. Translocation carrier 21

<i>Maternal age</i>	<i>Risk</i>
All ages	1:650
20	1:1530
30	1:1000
35	1:365
40	1:100
45	1:50

Carrier father rarely affect the offspring, they do produce both normal and carriers.

If one parent is mosaic, the risk depends upon the degree of gonadal of mosaicism of the affected. Paternal age increases the risk of Down syndrome after the age of 55 years. The recurrence risk for families, G-banded karyotype analysis is recommended as the study of choice. The recurrence risk for translocation carriers is higher and depends on the chromosomes involved in the translocation and the sex of the parent carrying the rearrangement.

## TREATMENT

### Medical Management

Patients are at higher risk of a number of problems and hence they should be screened for congenital heart defects, evidence of hypothyroidism and ophthalmological problems. The medical management depends upon the age of the child.

Most of the Down syndrome babies are hypotonic and many may have congenital heart defects. Feeding problems should be anticipated and managed appropriately. Breastfeeding should be encouraged as the baby will have upper respiratory tract infection, atopic disease and allergy.

Congenital cardiac defects are common and every child should have echocardiogram soon after the birth. All these heart defects should be managed in exactly the same way as any other child with congenital heart defects. In the absence of cardiac defects many children will have long life.

Duodenal atresia is most commonly encountered gastrointestinal abnormality. There is high incidence of Hirschsprung's disease and tracheoesophageal fistula. Constipation can be a major problem and Hirschsprung's disease should be suspected if it is severe. Celiac disease should also be kept in mind with a high index of suspicion.

These children may get recurrent upper respiratory tract infection and glue ears because of reduced cell-mediated immunity and hypertrophied tonsils and adenoids. Many of these may also develop significant hearing impairment for which they should be tested periodically.

Congenital cataracts should be detected at birth initially by routine examination for red reflex. Dense cataract should be removed as soon as possible. All children should be monitored for glaucoma periodically. Children may develop refractive errors and should be taken care.

Hypotonia may predispose to delayed motor milestones. These children may get benefit from regular physiotherapy. Global developmental delay becomes evident once the child grows. Speech and language milestones may be delayed. Growth of these children should be plotted on Down syndrome growth charts rather on regular centile charts.

Developmental dysplasia of hip occur due to hypotonia and joint laxity. This can lead to morbidity. About 15% of children with Down syndrome have radiological evidence of instability of atlantoaxial joint.

*Recommended health checkup for children with Down syndrome:*

1. Physical examination	At birth, 4 weeks, 8 weeks, 6 months and then annually
2. Eye checkup	Birth, 6 months, 1 year and then once in every year
3. Hearing assessment	Birth, 6 months and annual checkup
4. Thyroid function test	Birth, 3 months, 6 months and then every year

## COUNSELING

### Antenatal Counseling

Parents should be aware of screening and definitive tests that are available. They need to understand that a screening test places them in a higher or lower risk group but does not definitely diagnose or exclude Down syndrome. When it is diagnosed by amniocentesis or CVS the parents need to be informed of their choices. Genetic counseling about the recurrence risk should usually be delayed the couple have had time to deal with the immediate issues related to the current diagnosis of Down syndrome.

The diagnosis at birth should be explained in general terms. Parents should be allowed to clear all their medical doubts. One should offer emotional support to known problems and associated disorders and importance of early intervention.

### Genetic Counseling

This is done only after chromosomal analysis. The main indication is for recurrence risk and

information regarding future pregnancies. The recurrence risk depends upon the mother's age. As a guide the recurrence risk for women less than 30 is 0.7%. The recurrence risk for women over 30 is same as any other women of the same age.

### *Health Maintenance Guidelines*

- *Birth to 1 year:*
  - Karyotype confirmation and genetic counseling—newborn period
  - Cardiac evaluation and echocardiogram—newborn period
  - Confirm red reflex—newborn period
  - Check neonatal thyroid screen—newborn
  - Audiology (hearing and tympanometry)—by 6 months
- *1–12 years:*
  - Thyroid function tests—yearly
  - Vision evaluation—by 1 year
  - Audiology—yearly
  - ENT
  - Cardiac
  - Gastrointestinal
  - Neurodevelopment
  - Dental evaluation at 3 years, then twice yearly
  - Cervical spine X-ray
- *12–18 years:*
  - Thyroid function tests—yearly
  - Hearing and tympanometry
  - Vision to be checked
  - Cervical spine X-ray

### **Developmental Intervention**

This includes:

- Infant stimulation program
- Physical therapy
- Occupational therapy
- Parent support group

There will be reduction in linear growth rates, with height 2–4 SD below the mean for the general population. Adolescent growth spurt usually occur later. The final height for males ranges from 140 to 160 cm and for female between 135 and 150 cm.

The onset and progress of puberty is the same, or only slightly delayed for adolescent males with Down syndrome. Male typically show decreased penile length and testicular volume, though serum testosterone levels appear normal throughout puberty. Reduced sperm count and lack of mature sperm are the cause of infertility. Females of child bearing age should be considered as fertile.

Life expectancy has increased in recent decades to 50–55 years with proper health care. Neuropathologic hallmarks of Alzheimer disease (senile plaques, neurofibrillary tangles) are present in brains of nearly all individuals with Down syndrome by age 40 years. This is presumed to be secondary to the extra dosage of the amyloid precursor protein (APP) gene on chromosome 21. APP duplication has been reported in families with autosomal dominant Alzheimer disease. Premature dementia is found in about one-third of the Down syndrome population by age 60, with an estimated lifetime prevalence of 90% for all people with Down syndrome.

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# Klinefelter Syndrome

## PRESENTING COMPLAINTS

A 13-year-old boy was brought with the complaints of:

- Bilateral enlargement of breast—6 months
- Abnormal social behavior—6 months

## History of Presenting Complaints

A boy aged about 13 years was referred to the general surgeon for the management of the bilateral enlargement of the breast. According to the boy, he had noticed the enlargement of the breast for the last 6 months. But there was no discharge. He told that he had normal pubic hair development. Mother also told that his son used to be shy at the social gathering. School performance of the boy was rated as poor. School class teacher had also noticed the abnormal social behavior

among his classmates. He was fighting with his peers for trivial cause.

## Past History of the Patient

The boy was the third sibling of the consanguineous union. He was born at term by normal delivery. There was no significant postnatal event except for normal physiological jaundice. He was discharged on 3rd day. He was on breast milk soon after the delivery. Weaning started by the 4th month of the child. His developmental milestones were within normal range.

There was no family history of similar problems. His two older brothers were married with two children each. Those children were doing well.

## EXAMINATION

On examination, child looked tall, poorly built and undernourished. His height was on 50th centile for the age, the weight was below 20th centile. His height was 155 cm, the weight was 34 kg. His arms and legs were disproportionately long. He was quietly sitting on the examination table. There was bilateral gynecomastia. The diameter of the breast tissue was 5 cm.

The boy was afebrile, the pulse was 86 per minute, the respiratory rate was 18 per minute, and blood pressure was 110/70 mm Hg. There was no pallor, no edema and lymphadenopathy. There was no icterus and clubbing.

Per abdomen examination revealed, the small size of the testicle, i.e., 1.8 cm in length (normal 5.1 cm) and smaller phallic length, i.e., 5 cm (normal 6.5 cm). Pubic hair development was in feminine pattern.

Developmental assessment of the child showed retarded growth in all the parameters such as mental, social and behavioral quadrants. His intelligence quotient was 15–20 points below the other siblings. Other systemic examinations were normal.

### CASE AT A GLANCE

#### Basic Findings

Height	: 155 cm (50th centile)
Weight	: 34 kg (20th centile)
Temperature	: 37°C
Pulse rate	: 86 per minute, regular
Respiratory rate	: 18 per minute
Blood pressure	: 110/70 mm Hg

#### Positive Findings

##### History

- Bilateral enlargement of breast
- Poor school performance
- Behavioral problems

##### Examination

- Tall and poorly built
- Small testes and phallus
- Gynecomastia
- Behavioral disturbance

##### Investigation

- *Karyotyping*: 47,XXY
- *FSH*: Increased
- *LH*: Increased
- *Plasma testosterone*: Decreased
- *Plasma estradiol*: Increased
- *Semen analysis*: Azoospermia

## INVESTIGATION

Hemoglobin	: 13 g/dL
TLC	: 7,800 cells/cu mm
ESR	: 30 mm at the 1st hour
Chest X-ray	: Normal
FSH	: 5.2 U/L (Normal 1.8–3.2 U/L)
LH	: 6 U/L (Normal 0.2–4.9 U/L)
Plasma testosterone	: 0.5 nmol/L (Normal 0.62–5.20 nmol/L)
Plasma estradiol	: 200 pmol/L (Normal 2.9–128 pmol/L)
Serum prolactin	: 0.56 nmol/L (Normal 0.13–0.77 nmol/L)
Karyotype	: 47 chromosome with sex chromosome XXY, i.e., 47,XXY
Semen analysis	: Revealed azoospermia
Testicular biopsy	: Revealed hyalinized seminiferous tubular membrane and adenomatous clumping of Leydig cells. There was predominance of Sertoli cells

## DISCUSSION

It is a case of Klinefelter syndrome. There is a failure of development of secondary sexual characters and increased gonadotropins. This was described by Klinefelter, Reifenstein and Albright in 1942.

It is the most common sex chromosomal aneuploidy in males. The incidence is 1 in 1000. It is characterized by hypogonadism, small testes, failure of development of the secondary sexual characters and increased gonadotropins. It accounts for 10–20% of male infertility.

The classical description includes mental retardation, hypogonadism and gynecomastia. They are on an average 10 cm taller than XY males. The altered body proportion is with low upper to lower segment ratio.

Cells deviating from the multiples of the haploid number are called aneuploid, indicating a missing or extra chromosome. This occurs most often from the meiotic nondisjunction of an X-chromosome. In 54% it may be maternal in origin, and in 46% it is paternal in origin. These individuals have a male karyotype with extra X-chromosome, i.e., 47,XXY. The phenotype is male. When the number of X-chromosome exceeds two, mental retardation and impairment of virilization is more.

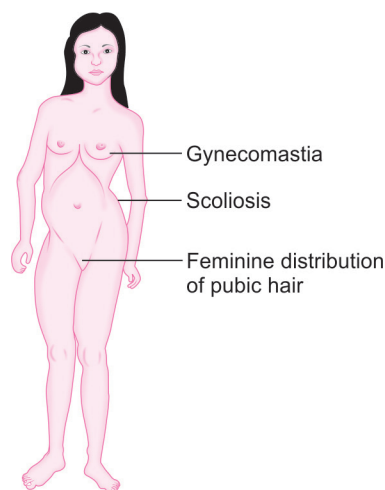
## CLINICAL FEATURES (FIG. 1)

These patients approach to the doctor, with the failure of development of secondary sexual characters. These patients tend to be tall and underweight. They have relatively elongated legs. The testes tend to be small for the age, and the phallus tend to be smaller than average. Cryptorchidism and hypospadias may also occur.

Development of the puberty is delayed. Feminine distribution of the pubic hair is present. Forty percent of the adults will have gynecomastia appearing usually soon after puberty between ages of 14 and 16 years. The most common testicular lesions are spermatogenic arrest and Sertoli cell predominance. The testes are small with the mean length of 1.8 cm as compared to 5.1 cm in normal male. The testes show normal growth early in puberty, but it stops in midpuberty. Testes are shrunken and hyalinized seminiferous tubules. Some are lined by Sertoli cells. Hypertrophy and clamping of Leydig cells is present. Azoospermia and infertility are encountered. Antisperm antibodies are detected.

The diagnosis is commonly made at puberty. This is because of subtleness of clinical manifestation in childhood. Other features such as behavioral or psychiatric disturbances, learning and school adjustment problems should be evaluated to rule out this syndrome. These children may be anxious, aggressive, and engage in antisocial acts. There will be verbal cognitive defects and underachievement in reading, spelling and mathematics.

There is increased incidence of pulmonary disease, varicose veins, cancer breast, diabetes



**Fig. 1:** Clinical features.

mellitus and peptic ulcers. Lymphomas and leukemias are associated. Extragonadal germ cell tumor especially of the mediastinum, cerebral hemangiomas occur with high frequency.

#### CLINICAL FEATURES IN BRIEF

- Infertility
- Small testes with hypogonadism
- Tall stature
- Gynecomastia at adolescence
- Normal pubertal development
- Normal range intelligence
- Educational and psychological problems

#### ESSENTIAL DIAGNOSTIC POINTS

- Microorchidism, normal external genitalia
- Azoospermia, sterility
- Gynecomastia, normal to borderline IQ
- Diminished facial hair, lack of libido and potency
- A tall eunuchoid build

#### GENERAL FEATURES

- Behavioral problems
- Psychiatric problems
- Delayed puberty
- Mental retardation
- Tall and slim
- Underweight
- Learning disabilities
- Antisocial acts

### DIAGNOSIS

It should be suspected in prepubertal children, who have long legs, smaller than normal testes, small phallus, learning disorders, delay in language development, mental retardation, or psychosocial behavioral problems.

Gonadotropins are elevated, testosterone levels are slightly low. Estradiol levels are elevated and account for gynecomastia. Chromosome analysis reveals 47,XXY karyotype.

Testicular biopsy shows deficiency and absence of germinal cells before puberty. After puberty seminiferous tubules are hyalinized and shrunken. There is adenomatous clumping of

Leydig cells. There is predominance of Sertoli cells.

#### LABORATORY SALIENT FINDINGS

- Gonadotropins are elevated
- Testosterone levels are slightly low
- Estradiol levels are elevated
- Chromosome analysis reveals 47,XXY karyotype
- *Testicular biopsy*: Deficiency and absence of germinal cells, seminiferous tubules are hyalinized and shrunken, adenomatous clumping of Leydig cells. Predominance of Sertoli cells

The testosterone concentration is low. The concentration of estradiol are normal or increased and gonadotropin concentration are elevated. Gynecomastia occur is 40–50% of cases as a result of increased ratio of serum estradiol to testosterone. Breast cancer occurs in 4% of patients and incidence is 20 times higher than in normal males.

### TREATMENT

Replacement therapy with long acting testosterone preparations are recommended. It should begin at 11–12 years of age. The enanthate ester may be used. The starting dose is 25–50 mg given intramuscularly every 3–4 weeks. The increment of 50 mg is done once in every 6–9 months till the maintenance dose of adult is obtained. The maintenance dose of adult is 250–300 mg every 3 weeks. Children XXY/XY mosaicism have better prognosis. As the number X chromosomes increases beyond two, the clinical manifestation increases correspondingly.

Management includes behavioral and psychological rehabilitation.

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# Turner Syndrome

## PRESENTING COMPLAINTS

A 12-year-old girl was brought by the mother with the history of:

- Not attaining secondary sexual characters—till now
- No enlargement of breast nodule—till now

## History of Presenting Complaints

A 12-year-old girl was brought by the mother with the history of not attaining the secondary sexual characters to the pediatric outpatient department. Her mother was complaining that there was not even small enlargement of the breast nodule. She told that her elder daughter had menses at this age.

## Past History of the Patient

The patient was the second sibling of the non-consanguineous marriage. She was born at full term by normal delivery. Patient's mother recalled her memory and told that patient had the swelling of the lower limbs at birth. For this doctor's consultation was sought. But the doctor told that it was not the significant observation. Apart from this there was no significant postnatal event. Child was fed with the breast milk after the delivery. There was no delay in the developmental milestones. Child had been completely vaccinated.

Child used to have repeated discharge in the ears throughout her childhood. This has led to the hearing difficulty in the left ear. Her scholastic performance was rated an average. There was no family history of similar complaints.

### CASE AT A GLANCE

#### Basic Findings

Height	: 126 cm (3rd centile)
Weight	: 36 kg (30th centile)
Temperature	: 37°C
Pulse rate	: 86 per minute
Respiratory rate	: 16 per minute
Blood pressure	: 90/70 mm Hg in upper limb 86/60 mm Hg in lower limb

#### Positive Findings

##### History

- No secondary sexual characters
- Short stature
- Ear discharge
- No similar complaint in family

##### Examination

- Short stature
- Webbing of the neck
- Broad chest
- Cubitus valgus
- No secondary sexual character
- Hearing difficulties

##### Investigation

- Karyotype 45,XO
- Short metacarpal and metatarsal bone
- Ultrasound abdomen
- FSH—raised

## EXAMINATION

Child was sitting shy on the examination table. She was short. Her height was 126 cm (3rd centile) and weight was 36 kg (30th centile). There was no pallor, no lymphadenopathy, no clubbing and no cyanosis.

She was afebrile. Pulse was 86 per minute. All the peripheral pulses were felt. The respiratory rate was 16 per minute and was regular. The blood pressure recorded in the upper limb was 90/70 mm Hg and in the lower limb was 86/60 mm Hg. Webbing of the neck was present. Chest appeared broad with widely spaced nipple. Cubitus valgus was present. There were short fourth metacarpal and metatarsal bones. The discharge was present in the left ear. There was hearing defect. Cardiovascular system examination was normal. There was no evidence of the murmur. Abdominal examination did not reveal any mass. No secondary sexual characters were present.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 7,500 cells/cu mm

ESR	: 20 mm in the 1st hour
Absolute eosinophil count	: 330 cells/dL
Chest X-ray	: Normal
Skull X-ray	: Normal
X-ray of hand and foot	: Short metacarpal and metatarsal bone
KUB	: Normal
Ultrasound abdomen	: Revealed streak ovaries
Karyotype	: 45,XO
FSH	: 3.6 U/L (1.8–3.2U/L)

## DISCUSSION

Short child with no secondary sexual characters and above clinical and laboratory finding suggests the diagnosis of Turner syndrome. Turner syndrome was described in 1938 by Dr Henry Turner.

Turner syndrome has 45 X-chromosomal complement. The mechanism of the loss of chromosome is unknown. The genes involved in Turner phenotype is X-linked genes.

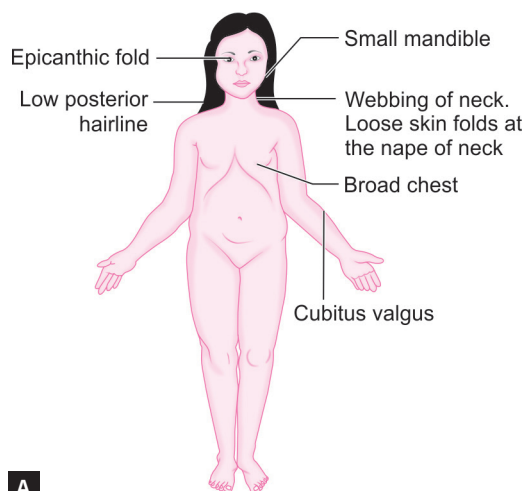
Turner syndrome occurs in 1 in 2,500 live born females. In the absence of the X-chromosome, oocyte present in the ovary starts disappearing by the age of 2 years. The ovaries become streak ovaries in the absence of the oocytes. The majority of the 45 X-chromosome fetuses are likely to be aborted. There will be considerable degree of chromosomal mosaicism, i.e., 45,X/46,XX. Formation of isochromosome of long arms of X-chromosome may lead Turner phenotype with 46 chromosome because of absence of short arms. It occurs due to errors in postzygotic mitosis. The single X-chromosome is often maternal.

## CLINICAL FEATURES (FIGS. 1A TO D)

Most of them can be diagnosed at birth. These newborn will have characteristic edema of the dorsum of the hands and feet, loose skin folds are present at the nape of the neck. This is commonly seen among low birth weight babies.

The clinical features depend on chromosomal constitution of the individuals. The patients with 45,X Turner syndrome show many characteristic somatic abnormalities. Whereas those with mosaicism and structural abnormalities of X-chromosome (variant Turner syndrome) show minimal somatic abnormalities. However, short stature, streak ovaries are constant findings.

In childhood, the child is short-stature. Short neck, webbing of the neck, low posterior hairline,



**A**



**B**



**C**

**D**

**Figs. 1A to D:** (A) Clinical features; (B) Lymphedema of feet; (C) Low hair line; (D) Short neck.  
(For color version (Figs. B to D) see Plate 1)

small mandible, epicanthic fold, high arched palate, broad chest with widely spaced nipple are present. Cubitus valgus is also the feature. Bony anomalies include medial tibial exostosis, short fourth metacarpal and metatarsal are present. Sexual maturation fails to occur at puberty. Adult height will be less than 145 cm. It has been recommended to consider Turner syndrome in all girls with short stature.

#### ESSENTIAL DIAGNOSTIC POINTS

- Webbed neck edema of hands and feet
- Coarctation of aorta
- Short stature shield chest, wide set nipples
- Streak ovaries, amenorrhea
- Absence of secondary sexual characters
- Infertility
- Malformation of urinary tract

Associated clinical features include the abnormalities of cardia, renal and of the ears. Cardiac abnormalities include coarctation or aorta, aortic stenosis, mitral valve prolapse, and anomalous pulmonary venous drainage. Renal abnormalities include pelvic kidney, horseshoe kidney, double collecting system, absence of one kidney and ureteropelvic junction obstruction. There will be perceptive hearing defects. This occurs as a result of the recurrent otitis media. Hypothyroidism occurs in 15–30% of adults with Turner syndrome.

Congenital lymphedema recedes in early infancy leaving only puffiness over the dorsum of the fingers and toes. Antithyroid antibodies are also present among 30–50% of patients. Crohn's disease, ulcerative colitis, gastrointestinal bleeding, scoliosis, karatoconus, pigmented nevi and alopecia occur.

#### CLINICAL FEATURES IN BRIEF

- Persistent lymphedema of hands and feet
- Short stature—cardinal feature
- Webbing of neck or thick neck
- Cubitus valgus—wide carrying angle
- Widely spaced nipples
- Congenital heart disease (CHD)—coarctation of aorta
- Delayed puberty
- Ovarian dysgenesis—infertility
- Renal agenesis
- Hypothyroidism
- Recurrent otitis media
- Renal anomalies
- Normal intellectual

At puberty, may present for the first time with primary and failure of secondary sexual

development. Streak gonads are found with ultrasound and at laparotomy. The patients are almost invariably sterile. But menstruation and secondary sexual developmental may be induced by estrogen replacement. Girls with Turner syndrome have a normal life span. Hypertension and osteoporosis may be present in adult life.

Sexual maturation fails to occur. Spontaneous breast development is seen among 20%. The increased incidence of the premature menopause and increased risk of miscarriage occur.

#### GENERAL FEATURES

- High arched palate
- Coarctation of aorta
- Horseshoe kidney
- Double collecting system
- Goiter

#### LABORATORY SALIENT FINDINGS

- Chromosomal analysis
- Ultrasonography of the heart, ovaries, and kidneys
- *Gonadotropins*: FSH is elevated

### DIAGNOSIS

Chromosomal analysis should be considered. Ultrasonography of the heart, ovaries and kidneys are indicated, skeletal abnormalities include shortening of the fourth metatarsal and metacarpal bones, epiphyseal dysgenesis and scoliosis. Gonadotropins especially follicle-stimulating hormone (FSH) is markedly elevated. Thyroid antibodies should be checked.

### DIFFERENTIAL DIAGNOSIS

This includes lymphedema, congenital syphilis and congenital nephrotic syndrome.

### TREATMENT

Treatment is with:

- Growth hormone therapy
- Estrogen replacement therapy for the development of secondary sexual characters at the time puberty.

The growth hormone replacement is considered once there is evidence of growth velocity attenuation. The dosage is 0.375 mg/kg/week. The improved growth is seen if it is started at 12–13 years. It may increase the final height of 8–10 cm.

Cyclic estrogen and progesterone therapy in phenotype female at prepubertal age, i.e., 14 years

will improve physical development, induce regular menstrual cycles and thus have great psychological benefit. An anabolic steroid—oxandrolone in very low doses of 1.25 mg daily is helpful to accelerate growth rate and increase adult height.

Premarin is a conjugated estrogen. The dose is 0.3 mg/day or ethinyl estradiol 5–10 mg/day given daily for 3–6 months. It is effective in inducing puberty. Then the dose is increased to 0.625–1.25 mg of conjugated estrogen or 20–50 µg/day of ethinyl estradiol. Cyclical therapy with estrogen and progesterone is started after 6–12 months. Prophylactic gonadectomy is advised for Y-chromosome patients due to risk of gonadoblastoma.

Cardiac evaluation is recommended periodically. Regular measurement of blood pressure at baseline and every year is advised. Renal malformations should be evaluated ultrasonographically. Regular audiometry is advised in adulthood.

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# Bronchial Asthma

## PRESENTING COMPLAINTS

A 7-year-old boy brought with the complaints of:

- Cough since 2 days
- Vomiting since 1 day
- Breathlessness since 2 hours
- Tiredness since 2 hours

## History of the Presenting Complaints

A 7-year-old boy was brought to the emergency room early with the history of persistent cough, breathlessness and tired. According to the mother, his son went to sleep without any symptom. She revealed later that cough was present since 2 days. Cough was dry irritating type. There was history of vomiting as a result of the cough. According to the mother, there was disturbance of sleep and appetite was decreased to certain extent. The child was shown to the general practitioner.

### CASE AT A GLANCE

#### Basic Findings

Height	: 122 cm (50th centile)
Weight	: 24 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 150 per minute
Respiratory rate	: 60 per minute
Blood pressure	: 90/70 mm Hg

#### Positive Findings

- Persistent cough
- Breathlessness
- Vomiting
- Disturbance of sleep
- Family history of bronchial asthma
- Treatment with nebulization

#### Examination

- Dyspnea
- Tachycardia
- Tachypnea
- Indrawing and retraction of chest
- Wheeze
- Hepatomegaly

#### Investigation

- No abnormal findings

## Past History of the Patient

He was the second child of the nonconsanguineous marriage. He was born at term by normal vaginal delivery. He cried immediately after the birth. The birth weight of the child was 2.9 kg. He was on breast milk exclusively for the 4 months of age. Weaning started by the age of 4 months and was completed by 13 months. He had been vaccinated completely.

There was strong family history of father being suffering from wheezing. He was on regular inhaler for the chronic management. This child had developed wheezing recently. He was symptomatic to treatment with the bronchodilator and nebulization.

## EXAMINATION

On examination, he was moderately built and moderately nourished. Anthropometric measurements included that his height was 122 cm (50th centile), the weight was 24 kg (50th centile).

He was afebrile, dyspneic and was more comfortable on sitting. He was sitting bending, his body forward keeping, his hand over the thigh. Pulse rate was 150 per minute and the respiratory rate was 60 per minute. Chest retraction and indrawing of the ribs were present. The blood pressure recorded was 90/70 mm Hg. There was no pallor, no cyanosis, and clubbing. There was no significant lymphadenopathy.

Respiratory system revealed the presence of the rhonchi, wheeze throughout the lung fields. Per abdomen examination showed the presence of nontender hepatomegaly. Cardiovascular system revealed tachycardia.

## INVESTIGATION

Hemoglobin	: 11 g/dL
TLC	: 8,800 cell/cu mm
DLC	: $P_{72} L_{18} E_8 M_2$
ESR	: 24 mm in the 1st hour
AEC	: 400 cells/cu mm
Chest X-ray	: Normal

## DISCUSSION

A child was brought with the history of breathlessness and tiredness. There was strong family history of the bronchial asthma. The child was having nebulization for the relief of the wheeze. On examination there was tachypnea, hepatomegaly and presence of wheeze confirms the bronchial asthma.

Bronchial asthma is a chronic inflammatory disease of airways affecting 15–20% of children. Diagnosing asthma in preschool children is often difficult. Nearly 50% of children will have wheeze during first 3 years of life. In general, there are two types of wheezing:

1. Transient early wheezing
2. Persistent and recurrent wheezing

### Transient Early Wheezing

This is also known as episodic viral wheeze and wheezy bronchitis. This occurs as a result from small airways being narrowed and obstructed due to inflammation and aberrant immune response to viral infection. This is more common in males and usually resolves by 5 years of age.

### Persistent and Recurrent Wheezing

Preschool and school-aged children will have frequent wheeze triggered by many factors. Here immunoglobulin E (IgE) is present common to inhalant allergens. Recurrent wheezing associated with evidence allergy, i.e., skin prick test or IgE blood test is termed “atopic asthma”. These have persistent symptoms and decreased lung functions. They are strongly associated with eczema, food allergy, rhinitis and conjunctivitis.

There is increased responsiveness of the trachea and bronchi to the various stimuli. Bronchial reactivity is the essential component of bronchial asthma. There will be edema, excessive mucus production infiltration of cells like eosinophils, mast cells neutrophils and lymphocytes. There will be excessive secretion of the mucus, inflammatory cells and cellular debris. Smooth muscle spasm will also produce obstruction. This leads to the reversible widespread narrowing of airways which in turn leads to the airway obstruction. Airway obstruction manifests clinically paroxysmal dyspnea, wheezing and cough.

The various stimuli that trigger bronchial asthma may be of two types. One is extrinsic and second is intrinsic. Extrinsic is IgE-mediated. It is mainly allergen triggered. The intrinsic is

mainly infection triggered. It is also IgE-mediated. There is one more group. This is mixed and it is excessive and aspirin induced.

There will be biphasic response in the body to the allergy. This leads to bronchoconstriction. The biphasic response includes early reaction and late reaction.

Early reaction occurs within 10 minutes of exposure. Chemical mediators are released. These include histamine leukotriene C, D and E, prostaglandin, platelet activating factor and bradykinin. These are released from mast cells. Early reaction occurs due to interaction of mast cells bounded IgE with allergen. This causes bronchoconstriction, mucosal edema and mucosal secretion. This manifests airway obstruction.  $\beta_2$ -agonist drug with inhibit this phase.

Late reaction occurs within 3–4 hours. It reaches peak reaction by 8–12 hours. This occurs due to release of mast cell mediators. This phase cannot be inhibited by  $\beta_2$ -agonist drug. This is inhibited by premedication with steroids. This suggests mucosal edema and inflammatory reaction are the cause airway narrowing. This phase presents as clinical asthma.

There is imbalance between excitatory and inhibitory mechanism. Excitatory mechanism includes cholinergic, alpha-adrenergic and noncholinergic. Inhibitory mechanism includes  $\beta$ -adrenergic and nonadrenergic. This increases bronchial reactivity.

Bronchoconstriction results in increased cholinergic activity. This leads to bronchial smooth muscle spasm. Bronchodilatation occurs due to endogenous catecholamine and nonadrenergic system. These act through  $\beta$ -adrenergic receptors and prostaglandin  $E_2$ .

Some neuropeptides are secreted by nonadrenergic and noncholinergic nerves. These are vasoactive intestinal peptides substance P. These will relax smooth muscles of bronchi. These increase smooth muscle tone, mucus secretion and microvascular leakage.

In the early phases, dyspnea, i.e., breathlessness produces hyperventilation. This causes fall in  $\text{PaCO}_2$ . Alveolar hypotension supervenes when the obstruction becomes severe. This leads to retention of  $\text{CO}_2$ . Hence, there is rise in  $\text{PaCO}_2$ . With the exhaustion of buffer mechanism, pH of blood falls, respiratory acidemia occurs.

## PATHOGENESIS

Airway inflammation is the basic pathology. It occurs due to the hyperactivity of airways to a



variety of stimuli. It is initiated by degranulation of mast cells release of mediators of inflammation. This damages the airways leading to epithelial shedding and mucus secretion. It is characterized by repeated attacks of cough with respiratory distress. The respiratory distress reverses either spontaneously or with bronchodilators. It is the result of multifactorial inheritance.

The risk factors include family history of asthma, atopy and bronchiolitis in infancy. Passive smoking is a predisposing factor. The triggering factors include upper respiratory tract infection, cold air, exercise, chemical irritants and anxiety. This stimulate release of mediator from mast cells. Exclusive breastfeeding during the first 6 months will protect against the development of asthma to certain extent.

Viral infection triggers airway narrowing. It produces opening up of the tight intraepithelial cell junction. Integrity of mucosal surface is disturbed. This leads to the shelling of epithelium. Mucosal edema and mucosal secretion results with airway narrowing.

Exercise induces water loss. Water loss produces mucosal hyperosmolarity. This stimulates mediators released from mast cells. Sudden weather change may result in the loss of heat and water from the lower airways. There will be airborne allergen in the atmosphere. This results in exacerbation of bronchial asthma. Emotional factors act through the vagus nerve. This causes the contraction of smooth muscles.

## CLINICAL FEATURES (FIG. 1)

Symptoms vary from simple recurrent cough to severe breathlessness secondary to wheezing. Acute asthma may usually begin with cold or bouts of spasmodic cough. Symptoms worsen during evening or early morning or may be exaggerated by triggers, i.e., exercise, allergen exposure. Family history of asthma or allergy should be ascertained.

Cough is nonproductive in early phase. Later child becomes more breathless with prolonged expiration and wheezing. Accessory muscles of respiration become active. The child sweats profusely. Child looks fatigued and apprehensive. Cyanosis may appear. Child becomes restless.

In severe conditions, the child keeps his arm forward for support. Chest becomes hyper-resonant because of excessive air trapping. When the obstruction becomes severe, there is decreased air entry, break sounds become feeble. Wheezing will be absent. Cyanosis appears. This is not a good sign. Wheezing reappears as the child improves

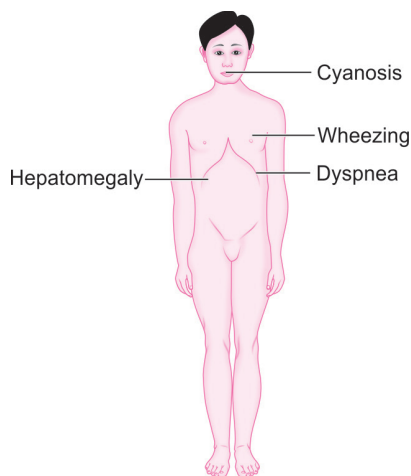


Fig. 1: Clinical features.

clinically and airflow increases. With the remission of attack wheezing disappear.

Cyanosis, cardiac arrhythmias, pulsus paradoxus indicate severe hypoxemia. Mucus plug blocks the bronchial tree and cause collapse of small segments of the lung. Chest becomes barrel shaped in chronic intermittent cases.

Presence of a wet cough or sputum, finger clubbing, or poor growth suggests chronic infections like bronchiectasis or cystic fibrosis.

The hallmark of bronchial asthma is wheezing. Wheezing is the whistling sound produced when the flow of air from the lung is obstructed. Obstruction may be due to the narrowing of the airway. This type of wheezing will respond positively to asthmatic therapy.

Wheezing can also be present in other diseases such as transient early wheezing, IgE-mediated atopic asthma, nonatopic asthma, cystic fibrosis, viral pneumonia, bronchiolitis, congestive cardiac failure, foreign body aspiration.

### GENERAL FEATURES

- Poorly built
- Persistent coughing
- Shortness of breath
- Rapid breathing

### ESSENTIAL DIAGNOSTIC POINTS

- Episodic symptoms of airway obstruction
- Wheezing, cough, breathlessness
- Reversible airflow obstruction

## DIAGNOSIS

Diagnosis of asthma is mainly by history and physical examination. The diagnosis of asthma

in infants and preschoolers is often difficult due to poor cooperation for diagnostic procedures, hesitation by pediatricians, time consuming and practicality and ethical issues. However, early diagnosis is essential for timely treatment to improve the quality of physical and psychological development, to prevent chronic pulmonary disease due to “airway remodeling” and educate on the preventive measures, in cut the healthcare cost and prognosticate.

## Preschoolers

The diagnosis of asthma is made based on national guidelines, who has more than three episodes of wheeze in 1 year with family history of asthma, has atopic features, afebrile episodes and cough persisting more than 2 weeks with good response to bronchodilators. In some children, a therapeutic trial of treatment with quick relievers and inhaled steroids for 8–12 weeks with good improvement and relapse after stopping treatment is diagnostic of asthma.

## School-going Children

- *Pulmonary function tests:* The diagnosis of asthma is clinical in most cases, hence pulmonary function tests may not play significant role. These investigations have an important role in diagnosis of doubtful cases and in monitoring the response to treatment. The important parameters in spirometry include peak expiratory flow rate (PEFR), forced expiratory volume in one second ( $FEV_1$ ), forced vital capacity (FVC) and  $FEV_{25-75}$ . All parameters are decreased in asthma.  $FEV_1$  is commonly used parameter for documentation of severity of asthma.  $FEV_{25-75}$  is effort independent and is probably more sensitive indicator of airway obstruction. PEFR can be measured easily with peak expiratory flow meter, while for other parameters spirometer is required. PEFR may be used as diagnostic tool in doubtful cases as well as monitoring of treatment. Abnormality in PEFR suggestive of asthma include: a diurnal variation of more than 20%, <80% of predicted and improvement of >20% after bronchodilator therapy.
- *Peak expiratory flow (PEF)* measurement before and after salbutamol nebulization with improvement (12–15%) is highly suggestive of reversible airway obstruction in asthma. This simple and less expensive procedure can be used to monitor the therapeutic response. Early asthma attack can be recognized by

measuring diurnal variation PEP. It measures the air coming out of larger and medium size airways.

- *Spirometry* is the central tool for defining the obstructive airway disease. In asthma there is decreased  $FEV_1$ ,  $FEV_1/FVC$  ratio and  $FEF_{25-75}$ .
- *Absolute eosinophil counts:* Significance of eosinophilia for distinguishing between allergic, vasomotor or infectious nature of the chronic respiratory obstructive disease is limited. When eosinophilia is present, bronchial obstruction generally responds well to antispasmodic therapy and the condition is often reversible. The eosinophil count may be low in cases associated with infection. Steroid medication in asthma causes eosinopenia.
- *Chest X-ray* shows bilateral and symmetric air trapping in case of asthma. Patches of atelectasis of varying sizes due to mucus plugs are not unusual. Main pulmonary artery is prominent due to pulmonary hypertension. Bronchial cuffing may occur due to the presence of edema fluid in perivascular and peribronchial interstitial space. Extensive areas of collapse or consolidation should suggest an alternative diagnosis. Chest X-ray film may often be normal.
- *Allergy tests include* skin test and radio-allergosorbent allergen-specific IgE (RAST) have limited usefulness. Few children need skin tests to identify sensitivity to different antigens since the role of desensitization therapy is not established.
- *Skin-prick testing:* This is often considered both as an aid to diagnosis of atopy and to identify allergens which may be acting as triggers. *Skin testing* with allergens is the gold standard to identify the specific allergens and used before immunotherapy for aeroallergens.
- *Total IgE level:* It is beneficial only to recognize the atopic background of asthma. It helps to predict a response to steroids, the prognosis and the possibility of development of persistent as well as strongly advocate environment control.
- *Specific IgE level:* It is needed for specific immunotherapy and before the use of anti-IgE antibody treatment.
- *Breath nitric oxide* is used in some pulmonary centers for monitoring the eosinophilic airway inflammation. It is not used much in children for various reasons.

Bronchial challenge tests and other physiological tests do not have a major role in the diagnosis of asthma in children.



A prolonged whistling sound heard at the mouth during expiration is called a wheeze. Recurrent attacks of wheezing indicate bronchial asthma. Although intermittent attacks of coughing may be due to recurrent viral infections, the diagnosis of bronchial asthma should be considered. Cough, which is associated with asthma generally, worsens after exercise. Sputum is generally clear and mucoid but expectoration of yellowish sputum (attributed to large number of eosinophils) does not exclude the diagnosis of asthma. Chronic spasmodic cough may suggest occult asthma.

## DIFFERENTIAL DIAGNOSIS

- *Bronchiolitis* always occurs within the first 2 years, usually within the first 6 months of life. It is more common in winter or spring months. Generally there is a single attack. Repeated attacks indicate viral infection-associated wheeze or asthma. Hyperinflation of chest with scattered areas of infiltration may be seen on chest X-ray. Asthma may start at any age; more than three episodes are usual and wheezing is prominent. Infants diagnosed as bronchiolitis with family history of allergy, having atopic eczema or whose IgE levels are elevated are likely to develop asthma.
- *Congenital malformation* causing obstruction, e.g., vascular rings such as aberrant right subclavian artery or double aortic arch, bronchogenic cysts and tracheomalacia should be excluded in differential diagnosis.
- *Aspiration of foreign body*: Wheeze, if present is generally localized. The history of foreign body aspiration may be forgotten. An area with diminished air entry, with or without hyper-resonance on percussion especially in children, may be due to obstructive emphysema because of a check-valve type of obstruction due to the foreign body. Most children develop frequent infections in the lung around the foreign body.
- *Hypersensitivity pneumonitis*: An acute or chronic lung disease may be observed following inhalation of organic dust such as molds, wood or cotton dust, bird droppings, fur dust, grain or following exposure to certain chemicals or drugs such as epoxy resins, p-aminosalicylic acid (PAS), and sulfonamides. In the acute form of illness, these children show from fever, chills, dyspnea, malaise, aches and pain, loud inspiratory rales (crackles) at bases of lung and weight loss. X-ray chest shows

interstitial pneumonia. Bronchial markings are prominent. The levels of IgE antibodies to the specific antigen are increased. The skin test shows Arthus phenomenon with local hemorrhage, edema and local pain within 8 hours of the test. Diagnosis is established by lung biopsy.

- *Cystic fibrosis*: Children with cystic fibrosis may present with recurrent wheezing, but over a period of time they develop clubbing. There may be clinical evidence of mal-absorption. X-ray film may show evidence of hyperinflation, peribronchial cuffing and pneumonia. Diagnosis is established by estimating sweat chloride levels.

## MANAGEMENT OF ACUTE EXACERBATIONS

A stepwise approach is necessary for appropriate management. The steps in management are:

1. Assessment of severity and identification of life-threatening attack
2. Initiation of therapy
3. Assessment of response to initial therapy
4. Modification of or addition to therapy and referral

### Step 1: Assessment of Severity and Identification of Life-threatening Attack

Initial assessment is necessary to rapidly determine the degree of airway obstruction and hypoxia. The features of a life-threatening attack of asthma are: (i) cyanosis, silent chest or feeble respiratory efforts; (ii) fatigue or exhaustion; (iii) agitation or reduced level of consciousness.

Any child with features suggestive of a life-threatening attack should ideally be treated in a hospital where intensive care facilities are available. However, the child should receive oxygen, bronchodilator and a dose of steroids before making arrangements for transfer to a tertiary level health facility. Oxygen and inhalation therapy (MDI with Spacer) should be continued while the child is being transferred.

### Identification of Life-threatening Attack

The features of life-threatening asthma are:

- Cyanosis
- Silent chest
- Poor respiratory effort
- Exhaustion
- Fatigue
- Altered sensorium
- PEF < 30%
- Oxygen saturation < 90%

Categorization of an acute exacerbation of asthma into mild, moderate or severe can be done based on physical examination and objective parameters as shown in **Table 1**. In any child with severe degree of respiratory distress, presence of alteration of sensorium confusion, and cyanosis will suggest respiratory failure. Examination needs to be repeated after each step of treatment of assess the response.

An objective measurement of lung function tests becomes necessary. The two methods of objective measurements of lung function that can be used are (i) measurements of airflow obstruction by PEFR or FEV<sub>1</sub>, and (ii) arterial blood gas (ABG) analysis or pulse oximetry.

Peak expiratory flow rate can be measured using a simple peak flow meter. A child is made to use the peak flow meter in a standing position, three times and the best of the three values is taken as the child's PEFR during the acute attack. This is compared with child's personal best or predicted PEFR.

It has been recommended that if pH is less than 7.3 or base deficit is greater than 5 mEq, intravenous correction with sodium bicarbonate is indicated, initially using half the calculated dose and then repeating the ABG.

Laboratory studies are generally not indicated in a routine acute exacerbation. However, if the child is unusually ill or there is a doubt of an infection, blood samples can be taken for (i) white blood cell count for detecting polymorphonuclear leukocytosis and bacteria which suggests bacterial infection, (ii) serum electrolytes since both beta-2

agonists and corticosteroids may cause hypokalemia.

A chest radiograph is indicated only when the diagnosis is doubtful or there is a suspicion of a foreign body. It is also useful in a child with high grade fever, localized crepitations, decreased breath sounds and other finding suggestive of infection or complications like pneumothorax, atelectasis and pneumomediastinum.

## Step 2: Initiation of Therapy

### Principles of Therapy

The following are the broad objectives:

- The goal is to rapidly reverse the acute airflow obstruction with consequent relief of respiratory distress. This is achieved by repeated use of inhaled beta-2 agonists.
- Hypoxia is treated by proper oxygenation of all acutely sick children.
- Corticosteroids are added early in an acute attack if the response to inhaled bronchodilators is not satisfactory.
- Repeated clinical and objective assessment is done to evaluate the response to the above, add other drugs of necessary and also to detect impending respiratory failure at the earliest.

### Initial Therapy

**Oxygen:** All patients of acute severe asthma have some degree of hypoxia. Oxygen at the rate of 3–6 L/min should be started. The flow should be enough to maintain oxygen saturation above 92%.

**TABLE 1:** Estimation of severity of acute exacerbation of asthma.

Symptom/sign	Mild	Moderate	Severe
Respiratory rate	Normal	Increased	Increased
Alertness	Normal	Normal	May be decreased
Dyspnea	Absent or mild; speaks in complete sentence	Moderate; speaks in phrases or partial sentences	Severe; speaks only in single word or short phrases
Pulsus paradoxus	<10 mm Hg	10–20 mm Hg	20–40 mm Hg
Accessory muscle use	No or mild intercostals retractions	Moderate intercostals retractions with tracheosternal retractions, use of sternocleidomastoid muscle	Severe intercostals and tracheosternal retractions with nasal flaring
Color	Pink	Pale	Ashen gray or cyanotic
Auscultation	End expiratory wheeze only	Wheeze during entire expiration and inspiration	Breath sounds becoming almost inaudible
Oxygen saturation	>95%	90–95%	<90%
PaCO <sub>2</sub>	<35 mm Hg	<40 mm Hg	>40 mm Hg
PEFR	70–90% of predicted or personal best	50–70% of predicted or personal best	<50% of predicted or personal best

*Beta-2 Agonists (Table 2)*

The currently recommended standard bronchodilator therapy is repeated inhalations of beta-2 agonist aerosol. Salbutamol nebulizer solution (5 mg/mL) in the dose of 0.1–0.15 mg/kg diluted in 3 mL of normal saline is administered over a period of 10–15 minutes. It is preferable to use central oxygen supply at the rate of 6–7 L/min to run the nebulizer, at least initially, to avoid hypoxia. The dose can be repeated every 20 minutes for three times and the child reassessed after that. The rationale behind giving repeated doses of inhaled bronchodilators is that the bronchodilatation that follows the initial dose allows more distal deposition of drug particles during further dosing. This results in dilatation of smaller airways and the short dosing interval prevents any deterioration of clinical status in the intervening period.

Recent studies, however, suggest that continuous nebulization may be more effective than intermittent nebulization. This method of therapy can continue for a prolonged period without having to set up nebulization at regular intervals.

Patients are more likely to get acclimatized to continuous nebulization and therefore maintain a more constant breathing pattern. This would result in subsequent reduction of inspiratory flow and more peripheral deposition of inhaled bronchodilator aerosol. Recommended doses are 0.1–0.5 mg/kg/h via a delivery system comprising preferably of a constant infusion pump and central oxygen supply. Higher doses of  $3.4 \pm 2.2$  mg/kg/h have been used in ventilated patients.

Alternatively, metered dose inhaler (MDI) can be used with a spacer device to give repeated inhalations of beta-2 agonist. It is considered

**TABLE 2:** Drug dosages in children with acute attack of bronchial asthma.

Drug	Available form	Dosage
<i>Inhaled beta-2 agonist:</i> Salbutamol Metered dose inhaler	100 µg/puff	2 inhalations every 5 minutes for a total of 10–20 puffs, with 0.1–0.15 mg/kg dose up to 5 mg every 20 minutes for 1–2 hours (minimum dose 1.25 mg/dose)
Nebulizer solution	0.5% (5 mg/mL)	or 0.1–0.5 mg/kg/h by continuous nebulization (maximum 15 mg/h) or $3.4 \pm 2.2$ mg/kg/h in ventilated patients
<i>Terbutaline</i> Metered dose inhaler Nebulizer solution	250 µg/puff 10 mg/mL	Two inhalations every 5 minutes for a total of 10–20 puffs <20 kg 2.5 mg >20 kg 5 mg
<i>Systemic beta-2 agonists:</i> Epinephrine HCl  Terbutaline	1:1000 sol (1 mg/mL) 0.05% (0.05 mg/mL) solution for injection in 0.9% saline	0.01 mg/kg up to 0.3 mg subcutaneously every 20 minutes for 3 doses Subcutaneous 0.005 mg/kg up to 0.3 mg every 2–6 hours as needed. Intravenous bolus of 10 µg/kg over 30 minutes followed by intravenous infusion at the rate of 0.1 µg/kg/min. Increase as necessary by 0.1 µg/kg/min every 30 minutes. Maximum dose is 4 µg/kg/min
<i>Inhaled anticholinergics:</i> Ipratropium bromide Metered dose inhaler Nebulizer solution	20 µg/puff 250 µg/mL	Two inhalations every 5 minutes for a total of 10–20 puffs 1 mL diluted in 3 mL normal saline every 20 minutes for 1–2 hours. This may be mixed with salbutamol nebulizer solution or alternated with salbutamol
Aminophylline	80% anhydrous theophylline (250 mg/10 mL inj.)	Give a loading dose of 5–6 mg/kg and maintain at 0.9 mg/kg/h. If patient is already receiving theophylline, avoid bolus dose
<i>Prednisolone</i>	5, 10, 20 mg tablets	1–2 mg/kg/dose every 6 hours for 24 hours, then 1–2 mg/kg/day in divided doses every 8–12 hours for 5–7 days
<i>Hydrocortisone</i>	50 mg/mL inj	10 mg/kg intravenous bolus followed by 2.5–5.0 mg/kg q6h
<i>Methylprednisolone</i> <i>Magnesium sulfate</i>	40 mg/mL inj 50% solution for injection (500 mg/mL)	4 mg/kg intravenous single dose 30–70 mg/kg in 30 mL N/5 saline intravenous infusion over 30 minutes

equivalent or better than nebulizer driven by compressed air. It does not cause oxygen desaturation unlike the former. The duration of therapy is less than a minute as compared to 15 minutes with a nebulizer. Use of MDI reduces the cost of therapy, is easily performed, and does not require power supply. One to two puffs every 5–10 minutes can be used for 10–20 times. One can use a commercially available large volume (750 mL) spacer device.

In some children with severe bronchospasm, an initial dose of epinephrine may be helpful prior to initiating inhalational treatment. Oxygen desaturation seen with nebulization therapy is not seen with this form of therapy. On the contrary transient increase in  $\text{PaO}_2$  has been noticed. Injectable terbutaline may also be used in place of epinephrine. Use of epinephrine is limited by its shorter duration of action, cardiac side effects and it cannot be repeated more than 2–3 times. Terbutaline has a longer duration of action and a repeat dose may not be required for 2–6 hours.

### *Anticholinergics*

Some studies have shown that concomitant use of inhaled anticholinergics and a selective beta-2 agonist produces significantly greater improvement in lung function than beta-2 agonist alone. Only ipratropium bromide is used in view of negligible side effects. As it has few systemic adverse effects, its use is advocated for patients with life-threatening features or those who do not respond to initial high dose inhaled beta-2 agonists.

Parasympathetic fibers are present in larger airways, in contrast to beta-adrenergic receptors which are located in more peripheral airways. Ipratropium may also have a generalized action throughout the lung. It being an acetylcholine antagonist while salbutamol is a beta-2 agonist, both acting at different sites in the lung and via different pharmacologic mechanisms, provides the basis for using these drugs together.

An optimal dose of 250  $\mu\text{g}$  contained in 1.0 mL of the respirator solution, may be mixed with salbutamol solution and both given together at an interval of 20 minutes with the nebulizer. It may also be given alternating with the dose of nebulized salbutamol. Dosing frequency may be reduced as the patient improves.

In patients who suffer from tachycardia or marked tremors in response to standard dose of beta-2 agonists and in younger age group (3–30 months) ipratropium may be more effective than salbutamol.

### *Corticosteroids*

Since inflammation is an important component of airway obstruction in an acute attack of asthma, there is no doubt that the use of steroids in an acute exacerbation is useful in resolving the obstruction. But it is somewhat difficult to decide precisely when steroids should be administered.

It is evident that the timing of initiation of steroid therapy plays a major role in the subsequent outcome of the attack. Studies have shown that the efficacy of steroid therapy is maximal when they are started soon after the patient presents in the emergency room. In contrast, benefits were minimal when steroids were initiated 24–48 hours after observation. A single dose of intramuscular methylprednisolone in a dose of 4 mg/kg, when given as an early adjunct to the beta-2 adrenergic therapy has been reported to reduce the hospitalization rates. In following situations, steroids should be started as soon as patient presents in the emergency:

- A child with a very severe attack of asthma.
- Previous history of life-threatening attack or severe attacks not responding to bronchodilators.
- If the child is on oral steroids or high doses of inhaled steroids for prophylaxis. An oral dose of 1–2 mg/kg of prednisolone may be as effective as an equivalent dose of hydrocortisone given intravenously, because the time for onset of action is the same. The total duration of therapy can be 3–7 days depending upon the response. However, children who have already been on long-term oral steroids would require a longer course with tapering of doses over 5–10 days.

### **Step 3: Assessment of Response to Initial Therapy**

Close monitoring for any signs of improvement or deterioration is important. The patient should be assessed after initial therapy of 2–3 doses of bronchodilator along with oxygen over a period of 1 hour. The plan for further management will depend on whether the response to initial therapy has been good, partial or poor.

### *Good Response*

The child with good response to initial therapy will become free of wheeze and have no breathlessness. Heart rate and respiratory rate will decrease. Auscultation of chest will show minimal or no rhonchi and PEF<sub>r</sub> or FEV<sub>1</sub> will improve

to more than 70% of the predicted best. Such a child can be observed in the emergency room for 2–4 hours and if remains stable, can be discharged on bronchodilators (inhaled or oral) for a period of 5–7 days. The parents should be advised to come for follow-up and all other necessary instructions should be given for prophylaxis.

### *Partial Response*

A child may show some response after bronchodilators, but may still have breathlessness and wheezing. Physical examination will reveal persistence of rhonchi. Heart rate and respiratory rate will be above the physiologic norms. Pulsus paradoxus of 10–15 mm Hg and oxygen saturation of 91–95% may be observed. PEER will be between 40 and 70% of the predicted normal. Treatment of a child with partial response is discussed later.

### *Poor Response*

If there is no subjective or objective improvement after initial therapy, it indicates a poor response. This child will continue to have severe respiratory distress and wheeze. Physical examination will reveal severe airway obstruction as indicated by significant pulsus paradoxus ( $\geq 15$  mm Hg), use of accessory muscles and extensive rhonchi. Oxygen saturation of  $\leq 90\%$  and PEER  $< 40\%$  of predicted normal may be observed.

## **Step 4: Modification of Therapy for Patients with Partial and Poor Response to Initial Therapy**

### *Continue Oxygen and Bronchodilator Therapy*

If the response to the initial therapy is not good, oxygen and beta-2 agonist inhalation should be continued. The frequency of inhalation should be decided according to the severity of respiratory distress. Children who do not have severe respiratory distress and have shown partial response may only require 2–4 hourly inhalation while children with severe distress should be given more frequent inhalations. Inhalation as frequently as every 20 minutes, or even continuous, can be given without side effects for the next 2 hours and child reassessed. If ipratropium is not used at the onset, it is added at the end of 1st hour as described earlier. MDI with a spacer can also be used frequently as an effective alternate device. It should also be ascertained whether the nebulizer and MDI are being used correctly.

### *Continue Corticosteroids*

Corticosteroids should be continued as 1–2 mg/kg/dose of prednisolone or 2.5–5.0 mg/kg/dose of hydrocortisone every 6 hourly.

### *Intravenous Fluids and Correction of Acidosis*

Children admitted with an acute severe attack of asthma often have mild to moderate dehydration. Dehydration may produce more viscous mucus, leading to bronchiolar plugging. Humidification of inspired air and correction of dehydration, therefore, are always indicated. However, at the same time, inappropriate hormone secretion has been reported in some cases of bronchial asthma. Hence, fluid therapy should be individualized to keep the child in normal hydration.

Hypokalemia has been reported with frequent beta-adrenergic and corticosteroid therapy. It should be corrected when present. Metabolic acidosis that occurs during an acute attack may decrease the responsiveness of bronchi to bronchodilators.

### *Monitoring*

If the child is very sick and is deteriorating, he may require continuous monitoring. Repeated assessments are necessary, at least at hourly intervals, in less sick children. PEFR or FEV<sub>1</sub> wherever possible, and ABG should be assessed for an objective evaluation especially in very sick and young children.

*Addition of other drugs:* If the patient has improved with continuation of the above therapy for about 2 hours, he can be observed for few hours and then discharged with proper advice. In case there is no improvement, treatment is intensified with addition of other drugs and the child is transferred to a place where intensive care facilities are available.

*Role of aminophylline:* The role of aminophylline in an acute attack of bronchial asthma is still controversial. There is no doubt that methylxanthines have bronchodilator activity but it is uncertain whether this adds to the bronchodilator effect achieved by beta-2 agonists and corticosteroids.

It is believed that aminophylline may act by mechanisms other than bronchodilation as well, such as stimulation of the respiratory drive, reduction in respiratory muscle fatigability and enhancement of mucociliary clearance.



A bolus dose depending upon previous treatment with methylxanthines is given followed by infusion of maintenance dose.

As soon as the patient shows response, aminophylline infusion may be substituted by injectable deriphyllin (6 hourly bolus) or even oral theophylline, if the patient is able to take orally.

**Intravenous terbutaline:** In children, with low inspiratory rates where nebulization of beta-2 agonists has failed, intravenous terbutaline, has been tried. Therapy is started with initial bolus of 10 µg/kg over 30 minutes, followed by an infusion at the rate of 0.1 µg/kg/min which may be increased by 0.1 µg/kg/min every 30 minutes, up to a maximum of 4 µg/kg/min or until there is a fall in PaCO<sub>2</sub>, with clinical improvement. Dose of terbutaline should be reduced by half, if theophylline is used concomitantly. Significant adverse effects noted with intravenous terbutaline are tachycardia, arrhythmias, hypertension, myocardial ischemia, hyperglycemia, hypokalemia, rhabdomyolysis, lactic acidosis, and hypophosphatemia.

**Magnesium sulfate:** Some patients with acute severe asthma, treated with in initial nebulization therapy with beta-2 agonists and corticosteroids may not improve and progress to respiratory failure. One drug which may be worth trying in these refractory patients, to avert mechanical ventilation, is magnesium sulfate. There is now evidence that magnesium sulfate can be given in children who failed to respond to initial treatment particularly if FEV<sub>1</sub> fails to rise above 60% at the end of 1st hour.

It acts by counteracting calcium-mediated smooth muscle contraction, through its influence on calcium homeostasis, inhibition of acetylcholine release at the neuromuscular junction inhibition of histamine release, direct inhibition of smooth muscle contraction and sedation. The recommended dose for infusion is 30–70 mg/kg over 20–30 minutes. It is available as a 50% solution, 0.2 mL/kg of which can be given as infusion in 30 mL N/5 normal saline in 5% dextrose over 30 minutes. There is also evidence that nebulized salbutamol administered in isotonic magnesium sulfate provides greater benefit than if it is delivered in normal saline. Serum levels greater than 4 mg/dL are necessary for bronchodilation. Onset of action occurs within a few minutes of intravenous infusion and lasts for 2 hours. Side effects include transient sensation of facial warmth, flushing, malaise and hypotension. At serum levels

greater than 12.5 mg/dL, side effects like areflexia, respiratory depression and arrhythmia may be noted, but this requires administration of doses greater than 150 mg/kg. Thus, it may be used as an adjunct to beta-2 agonist therapy, through its exact place in treatment of acute asthma remains to be determined.

## INTENSIVE CARE MANAGEMENT

### Indications for Transfer to an Intensive Care Unit

The patient is observed on above therapy for next few hours and is monitored frequently. The decision to transfer to intensive care unit (ICU) will depend upon the status of the child at the time of presentation and response to therapy. Any child with signs of life-threatening attack should be immediately transferred to ICU. If the child has been receiving therapy and has shown poor response after being observed for a few hours or develops clinical signs of impending respiratory failure like persistent hypoxemia, exhaustion or change in the level of sensorium, he should be immediately transferred to ICU. Continuous monitoring with the help of pulse oximetry or repeated ABG analysis is mandatory since most of these patients may not be in a position to perform PEF.

### Continuation of Therapy in ICU

The focus of care continues to be close observation and delivery of frequent nebulized beta-2 agonists, combines with corticosteroids and possibly aminophylline. As mentioned earlier, a trial of intravenous terbutaline and magnesium sulfate is desirable in a child who has not responded to above therapy due to low inspiratory flow rates.

### Intubation and Controlled Ventilation

Despite maximal pharmacologic therapy, some children do not respond favorably and require intubation and mechanical ventilation. The decision to ventilate is usually reserved as a last option.

Indications for mechanical ventilation include:

- Failure of maximal pharmacologic therapy
- Cyanosis and hypoxemia (PaO<sub>2</sub>, less than 60 mm Hg)
- PaCO<sub>2</sub> > 50 mm Hg and rising by more than 5 mm Hg/h
- Minimal chest movements
- Minimal air exchange
- Severe chest retractions

- Deterioration in mental status, lethargy or agitation
- Recumbent and diaphoretic patient
- Pneumothorax or pneumomediastinum
- Respiratory or cardiac arrest

ABG values alone are not indicative of the need for mechanical ventilation and should be interpreted in context of the clinical picture. It must be stressed that in spite of being aware of the morbidity that ventilation entails, it is better to intubate a child electively rather than to wait for cardiorespiratory arrest to occur.

The patient should be stabilized using 100% oxygen administered with a bag and mask. Oral and airway secretions should be cleared and stomach decompressed using nasogastric tube, to diminish risk of aspiration. Premedication with intravenous atropine and topical anesthesia to hypopharynx and larynx, helps to decrease bronchospasm and laryngospasm, which may be produced as a result of tipper airway manipulation.

An ideal sedative that may be used for intubation is intravenous ketamine in a dose of 1–3 mg/kg. The largest recommended endotracheal tube should be used. Muscle relaxation eliminates ventilator-patient asynchrony and improves chest wall compliance. It reduces  $\text{PaCO}_2$  for any given level of minute ventilation. Additionally, this gives the patient with respiratory muscle fatigue, a period of desperately needed physical rest. Vecuronium bromide, with an intermediate duration of action and without any cardiovascular or autonomic side effects, in a dose of 0.2–0.3 mg/kg may be used. Succinylcholine may be used too, but it has a short duration of action.

A volume cycled ventilator is recommended with low respiratory rate (8–12 per min) and long expiratory time (I:E ratio of 1:4 or 1:3) to prevent hyperinflation. Airway obstruction in itself causes intrinsic positive end-expiratory pressure (PEEP), therefore end-expiratory pressure (PEEP) should be minimal. Tidal volume of 10–12 mL/kg, and peak airway pressure less than 40–50 cm of water should be maintained. High inspiratory flow rates should be kept to improve gas exchange. This can usually be achieved with heavy sedation or use of muscle relaxants. Throughout ventilation, beta-2 agonists are nebulized into the inspiratory circuit of ventilator.

In the ventilated patients, therapeutic bronchoscope with lavage after administration of saline, sodabicarb and acetylcysteine has been used in very ill patients with persistent mucus plugging, to prevent atelectasis and nosocomial pneumonia.

### *Droperidol*

Dyspnea promotes anxiety, which may impair ventilation and interfere with efficacy of aerosol therapy. Therefore, in pediatric ICU setup, one may use safe sedatives with bronchodilator properties. Droperidol which has both of these properties may be used in asthmatics on assisted ventilation. It antagonizes bronchoconstriction mediated by alpha-adrenergic receptors in peripheral airways. Recommended dose is 0.22 mg/kg and its main side effect is hypotension.

### *Ketamine*

This drug is a dissociative anesthetic with excellent sedative and analgesic properties. It relaxes smooth muscle directly, increases chest wall compliance and also decreases bronchospasm in ventilated asthmatic children. It is given in a loading dose of 0.5–1.0 mg/kg, followed by an infusion of 1.0–2.5 mg/kg/h in ventilated children. The common side effects include arrhythmias, increased secretions and laryngospasm. It has been used in subanesthetic doses in nonventilated adults in ICU setup in the bolus dose of 0.75 mg/kg over 10 minutes, followed by an infusion at a rate of 0.15 mg/kg/h. Thus, intravenous ketamine can be used to relieve acute intractable bronchospasm, provided expert anesthetic help is available at hand.

## LONG-TERM MANAGEMENT OF BRONCHIAL ASTHMA

This includes identification and elimination of exacerbating of asthma or nocturnal cough, maintenance of near normal physical activity and parental education.

Effective long-term management includes:

- Identification and elimination of precipitating factors
- Pharmacological therapy

The goals of long-term asthma therapy include:

- To prevent chronic and troublesome symptoms, i.e., cough, breathlessness
- To maintain normal pulmonary functions
- To maintain normal activity levels
- To prevent recurrent exacerbation of attack

### Identification and Elimination of Precipitating Factors

Common factors associated with development and precipitation of asthma include passive smoking, associated allergic disorders, inadequate

ventilation at home leading to dampness, cold air, cold food, smoke, dust and pets in the family. Acute respiratory infection due to viruses is the most common cause of exacerbation of asthma.

Passive smoking exacerbates childhood asthma and removal from the exposure leads to the improvement in symptoms. It is better that one should not have pets, especially cats and dogs. Some food and additive may trigger attacks of asthma. Cold drinks, certain preservatives, nuts, shellfish, eggs have been associated with allergic response.

## Pharmacological Therapy

One should go in a stepwise manner. This can be achieved by following:

- Assessment of the severity of asthma
- Selection of medication
- Selection of inhalator device

**Assessment of severity:** Successful management of asthma requires grading the severity of the disease according to the frequency and severity of symptoms, functional impairment and PEFr. **Table 3** provides a guide to differentiate between mild episodic, mild persistent, moderate persistent and severe persistent asthma. After the assessment of severity, appropriate antiasthmatic drugs are selected.

It requires the grading the severity according to the frequency and severity of the symptoms and functional impairment. Pulmonary function tests by spirometer provides objective evidence of severity. PEFr measurement is an easy alternative to spirometry. It can be performed by the children older than 5–6 years of age.

Children with asthma can be classified into four groups:

1. *Mild episodic asthma* should be treated with inhaled or oral salbutamol or terbutaline as and when required.

2. *Mild persistent asthma.* Inhaled short acting beta-agonists are given as required. Additionally, these children need daily treatment with maintenance medication, i.e., inhaled (i) cromolyn sodium (5–10 mg 6–8 hourly); or (ii) steroids (budesonide or beclomethasone 400 µg/day or fluticasone 200 µg/day in two divided doses); or (ii) slow release oral theophylline 5–15 mg/kg/day in two divided doses. Drug selection is based on feasibility, toxicity, compliance and cost. The drug of choice in mild persistent asthma is a low dose inhaled steroid.
3. *Moderate persistent asthma.* Inhaled short acting β-agonists are given as required. Inhaled steroids (400–800 µg/day) are given in two divided doses. Long acting β-agonists (salmeterol) 50 µg once or twice a day can be added if needed. Sustained release theophylline is advocated in compliance to inhalation therapy is poor.
4. *Severe persistent asthma.* These children need inhalation steroids in the dose of 800–1200 µg/day 2–3 divided doses for relief of symptoms long acting β-agonist and/or slow release theophylline needs to be given regularly. Montelukast can be used at this step as add on treatment for better control of asthma symptoms. If there is persistence of symptoms, low dose alternate day oral prednisolone may have to be used.

**Bronchodilators:** This group of drugs provides immediate symptomatic relief. They may be short-acting and long-acting. The commonly used short-acting bronchodilators are adrenaline, terbutaline and salbutamol. Adrenaline is given subcutaneously. The other two agents can be administered by oral, inhalation or parenteral route. Inhalation route is preferred because of quick onset of action and least side effects. Long-acting beta-agonists include salmeterol and formoterol.

**TABLE 3:** Classification of asthma for long-term management.

	Symptoms	Night-time symptoms	PEFR
Severe persistent	Continuous Limited physical activity	Frequent	≤60% predicted, Variability >30%
Moderate persistent	Daily use β <sub>2</sub> -agonist Daily attack affect activity	>1 time a week	>60% <80% predicted, Variability >30%
Mild persistent	>1 time a week but <1 time a week	>2 times a month	≥80% predicted, Variability 20–30%
Mild intermittent	<1 time a week Asymptomatic and normal PEFr attack	≤2 times a month	≥80% predicted, Variability <20%

(PEFR: peak expiratory flow rate)



Adrenaline stimulates both  $\alpha$  and  $\beta$  receptors. It is given subcutaneously. Terbutaline and salbutamol are specific  $\beta_2$ -agonist and less cardiac side effects. It can be given by inhalation. The drawback of  $\beta$ -agonist is the lack of anti-inflammatory effect. So, although the symptoms are relieved, inflammation will aggravate bronchial hyper-responsiveness.

Long-acting  $\beta$ -agonists include salmeterol and formoterol. Both these drugs are specific  $\alpha$ -agonist and have a longer duration of action of 12–24 hours. The onset of action is delayed by 1/2–1 hour. Salmeterol offers prolonged bronchodilation and relief from need from short-acting drugs repeatedly.

In mild to moderate persistent asthma, inhaled salmeterol has been found to be superior to repetitive dose of salbutamol. However, it cannot be used as an adjunct to the inhaled corticosteroids. It appears to help in control of exercise-induced asthma. Formoterol is a full  $\beta_2$ -agonist. It is as effective as salmeterol and more rapid acting.

**Corticosteroids:** Asthma is a chronic inflammatory disease of airways. Corticosteroids being potent anti-inflammatory agents are the cornerstone of long-term treatment of asthma. The commonly used inhaled steroid includes beclomethasone, budesonide and fluticasone. Early interventions with inhaled corticosteroids after the diagnosis of asthma are made or after initial onset of symptoms, results in better response to treatment. This may be due to the influence of uncontrolled inflammation.

Being potent anti-inflammatory agents are the corner stone for the long-term treatment of asthma. Steroids inhibit cytokine production, inhibit cytokine receptors, affect various cells such as lymphocytes, eosinophils, neutrophils, macrophages, mast cells, etc.

Corticosteroids diminish the inflammation and bronchial hyper-responsiveness, as a result airway obstruction is reduced. The advantages of inhaled administration of corticosteroids is the application of the potent medication to the sites where it is specifically needed—airways and lungs. This reduces the risk of adverse reaction.

Optimal use of inhaled steroids necessitates the use of proper techniques with the use of metered-dose inhalers. Spacers result in better lung deposition. Use of spacers along with mouth rinsing after treatment reduces the amount of drug deposited in the oropharynx and swallowed. This results in lower of systemic side effects.

**Mast cell stabilizers:** The drugs included to their group are cromolyn sodium, nedocromolyn sodium and ketotifen. Cromolyn sodium reduces bronchial reactivity and symptoms induced by irritants, antigens and exercise. It is effective as theophylline in children. It diminishes IgE antibodies, induced release of inflammatory mediators from sensitized mast cells. It should be administered 3–4 times a day for good results. A recent study report suggests that it can be used in severe asthma in higher doses.

Nedocromil is another nonsteroidal drug used for the control of mild to moderate asthma. It is as effective as cromolyn in reducing exercise-induced symptoms and also reduces airway hyper-responsiveness to allergen challenge.

**Leukotriene modifiers:** Leukotriene inhibitors have an important role in the pathogenesis of asthma. They act either by decreasing synthesis of leukotriene or antagonizing the receptors. Leukotriene inhibitors are useful in the treatment of mild to moderate persistent asthma and exercise-induced asthma. Their main advantages are, they are given orally once a day and they do not induce tachyphylaxis.

Montelukast can be used in pediatric asthma patients who are more than 1 year of age. The pediatric dose is 5 mg once daily. Zafirlukast can be used above 12 years of age.

**Theophylline:** It is the oldest asthma medication. It has concentration-dependent bronchodilator effect. Bronchodilator effect is exerted by inhibition of phosphodiesterase. It has anti-inflammatory and immunomodulatory effects at therapeutic serum concentration. It has a role in long-term management of asthma. It can be alternative second-line therapy in combination of inhaled glucocorticoids in moderate persistent asthma in older children 5 years and younger. It is used as second-line therapy for mild persistent asthma in older children and adult. It is used as adjunctive therapy for the control of nocturnal symptoms in moderate severe persistent asthma.

**Immunotherapy:** This consists of giving gradually increasing quantities of allergen extract to clinically sensitive subject, so as to ameliorate the symptoms associated with subsequent exposure to allergen. This is considered in highly selected children who are sensitive-specific allergen. It is done under specialist supervision.

**Inhalation devices:** Drugs used by the inhalation route are more effective and have a rapid onset

of action, and fewer side effects. Also, smaller doses of the drug are needed to achieve the same pharmacological effect. Commonly available inhalation devices include: MDI, MDI with spacer, MDI with spacer with face mask, dry powder inhaler (DPI), and nebulizer.

- *Metered dose inhaler:* An MDI is a device, which delivers a fixed amount of medication in aerosol form each time it is activated. It can be used for exacerbation and maintenance therapy. They are effective but require considerable coordination, i.e., press and breathe coordination. This may not be possible in young children.

An MDI can be easily used for children above 10–12 years of age.

- *Metered dose inhaler with spacer:* use of spacer inhalation device with an MDI should be encouraged as it results in a larger proportion of the medication being deposited in the lung, with less impaction in the oropharynx. They also overcome the problems of poor technique and coordination of actuation and inspiration. Which occur, with the use of MDIs alone. Furthermore, use of spacer allows MDI to be used for younger patients. MDI used with spacer has been found to be comparable to nebulizer in delivering salbutamol in acute exacerbation of asthma in children. Spacer has the limitation of being bulky, relatively costly and cannot be used in young infants and toddlers. A home-made spacer prepared from mineral water bottle has been shown to be equally effective in delivering salbutamol in acute exacerbation.

A spacer can be easily handled by children more than 4 years of age. Attaching a face mask to the spacer facilitates their use in very young infants and children below 4 years.

- *DPI:* These are breath-activated devices like Rotahaler, Diskhaler, Spinhaler, Turbohaler and Accuhaler. They can be used in children above 4–5 years of age. They have the advantage of being portable and eliminate the need to coordinate actuation with breathing.
- *Nebulizer:* Nebulizer is an instrument by which the drug is delivered to the airways in form of very small drops. The required amount of drug is diluted with normal saline to make 3 mL of solution. The solution is put in the nebulizing chamber, which is run through a compressor. Alternatively, high oxygen flow (>5 L/min) through oxygen cylinders or central supply can be used to run the nebulizer. Repeated doses of this solution are given every 20 minutes. While giving therapy through nebulizer, it is mandatory to ensure that adequate visible vapors are being produced and the mask is held closely to child's face with minimal leak around the mask. In case the vapor production is deficient, the tubings and the nebulizing chamber should be checked for any leakage.

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## PRESENTING COMPLAINTS

An 8-year-old boy was brought with the complaints of:

- Cough since 6 months
- Bad odor since 6 months
- Fever since 1 week

## History of Presenting Complaints

An 8-year-old boy with the history of prolonged cough was brought to the pediatric outpatient department (OPD). The boy gave the history of cough since last 6 months. Cough used to be of productive type. He was spitting out the sputum. Sputum was mucopurulent, copious and foul smelling. Cough used to be more in the morning. The boy used to have disturbed sleep as a result of cough. This was associated with bad odor. Along with the cough, the child used to have

fever of moderate to high degree. This fever used to be relieved after a course of antibiotics and paracetamol. There was no history of breathlessness and chest pain.

## Past History of the Patient

He was the second sibling of a nonconsanguineous marriage. He was delivered at full term and delivery was uneventful. His developmental milestones were normal. He had been immunized completely. He had been treated for the primary complex at the age of 2 years. There was no family history of similar complaints. His sister was 10-year-old and maintained good health.

## EXAMINATION

On examination the boy was moderately built and nourished. He was alert and comfortable. Anthropometric measurements included, the height was 126 cm (70th centile) and the weight was 22 kg (50th centile). He was febrile, pulse rate was 100 per minute and respiratory rate was 26 per minute. Blood pressure recorded as 90/70 mm Hg.

He looked pale and clubbing was present. There was no edema and no lymphadenopathy. Respiratory system revealed the presence of coarse leathery crepitations, bronchial breathing, and percussion note was dull at basal region. Low pitched rattles were felt over the affected part of the chest. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 8 g/dL
TLC	: 21,000 cells/cu mm
DLC	: P <sub>80</sub> L <sub>18</sub> E <sub>2</sub>
ESR	: 26 mm in the 1st hour
Mantoux test	: Negative
ECG	: Normal
X-ray chest	: Honeycomb appearance suggestive of bronchiectasis
Spirometry	: Normal

### CASE AT A GLANCE

#### Basic Findings

Height	: 126 cm (70th centile)
Weight	: 22 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 100 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 90/70 mm Hg

#### Positive Findings

##### History

- Long duration cough
- Sputum
- Halitosis
- Bad odor
- Primary complex

##### Examination

- Clubbing
- Febrile
- Coarse crepitation
- Bronchial breathing

##### Investigation

- Anemia
- TLC increased
- X-ray chest: Honeycomb appearance

## DISCUSSION

It is chronic suppurative lung disease. It is characterized by destruction of the bronchial and peribronchial tissues and permanent dilatation of bronchi, resulting from airway obstruction by retained mucus secretions or inflammation in response to chronic or repeated infection. It occurs either as consequence of preceding illness, i.e., severe pneumonia foreign body aspiration or as manifestation of an underlying systemic disorder like cystic fibrosis, chronic aspiration and immunodeficiency.

Bronchiectasis may be either congenital or acquired.

Congenital bronchiectasis may be because of hypoplasia and developmental arrest of the bronchi. It occurs because of deficiency of bronchial cartilage and due to ciliary dysfunction. It is classified into three groups:

1. Tracheobronchial—it occurs due to hypoplasia and/or arrest of developmental arrest of bronchi. There may be tracheobronchomegaly—Mounsteir-Kunn syndrome. It may be deficiency of bronchial cartilage—Williams Campbell syndrome. In Kartagener syndrome—congenital bronchiectasis, sinusitis and situs inversus. This is due to ciliary dysfunction—immotile cilia syndrome. Young syndrome patients have sinusitis, bronchiectasis and azoospermia.
2. Vascular arteriolar aneurysm and pulmonary varies lead to mucosal congestion. These predispose to infection and hence bronchiectasis.
3. Lymphatic hypoplasia leads to poor lymphatic drainage and predispose to infection. Cystic fibrosis is an important cause. The cause may be thick secretion atelectasis and infection.

## CONDITIONS ASSOCIATED WITH BRONCHIECTASIS

- Cystic fibrosis
- Allergic bronchopulmonary aspergillosis
- Infections
  - Nontuberculous mycobacteria
  - Tuberculosis
  - *Pasteurella multocida*
  - Measles, adenovirus 21, pertussis
  - Human immunodeficiency virus
- Diffuse interstitial lung diseases: rheumatoid, Sjögren, idiopathic pulmonary fibrosis, sarcoidosis
- Primary immunodeficiency

- Post-lung transplantation
- Right middle lobe syndrome
- Pulmonary ciliary dyskinesia, Kartagener syndrome
- Postinhalation injury
- Ulcerative colitis
- Asthma
- Chronic obstructive pulmonary disease
- Alpha-antitrypsin deficiency
- Diffuse panbronchiolitis-bronchiectasis
- Yellow nail syndrome
- Young syndrome
- Swyer-James-MacLeod syndrome

Cystic fibrosis is the most common congenital cause of bronchiectasis in the developed world. In low- and middle-income settings, post-tuberculous and other postinfective causes should be considered.

Most of the cases are acquired. The basic pathology involves infection and obstruction. It is associated with the inflammatory destruction of the bronchial wall, peribronchial tissue and accumulation of exudative material in dependent bronchi.

Aspiration of foreign bodies, food and mucus plug in the bronchus may also produce obstruction and leads to segmental collapse. Multiple abscess may develop in the parenchymal and peribronchial tissue. Obstructive and arteritis of the small pulmonary vessels occur.

The most frequently affected lobes are right middle lobe segments, the basal segments of the lower lobes, the lingular segments of the left upper lobe. Aspiration of the foreign body involves right middle lobe. Hilar adenopathy frequently affects right middle lobe.

Due to infection, there is loss of ciliated epithelium. Later it is regenerated as cuboidal and squamous epithelium. The elastic tissue within the bronchial wall disappears and thickening occurs because of interstitial edema, fibrosis and round cell infiltration. Later bronchiectasis occurs in segmental distribution.

The infection could be because of measles, pertussis, pneumonia, bronchitis and bronchiolitis. The infection damages bronchial wall and segmental area collapse is caused. Negative pressure in the wall is exerted and dilatation occurs. The dilatation may be cylindrical, fusiform and saccular dilatation. These result in permanent dilatation. There are four main theories:

1. *Secretion theory*: Secretion obstruction and mechanically distend. Dilatation persists even after the clearance of the secretion.

2. *Traction theory*: Here infection leads to fibrosis and scarring. This exerts traction on bronchial wall.
3. *Atelectatic theory*: Collapse leads to increase in intrapleural pressure and hence dilatation.
4. *Infection theory*: Infection damages supporting structures of the bronchial wall and subsequently leads to bronchiectasis.

## CAUSES OF ACQUIRED BRONCHIECTASIS

- Measles, whooping cough, tuberculosis
- Pneumonia following adenovirus, herpes virus, and HIV
- Immunodeficiency state especially immunoglobulin G (IgG) and IgA
- Foreign body obstruction and lymph node compression producing middle lobe syndrome
- Chronic sinusitis

## CLINICAL FEATURES (FIGS. 1A TO C)

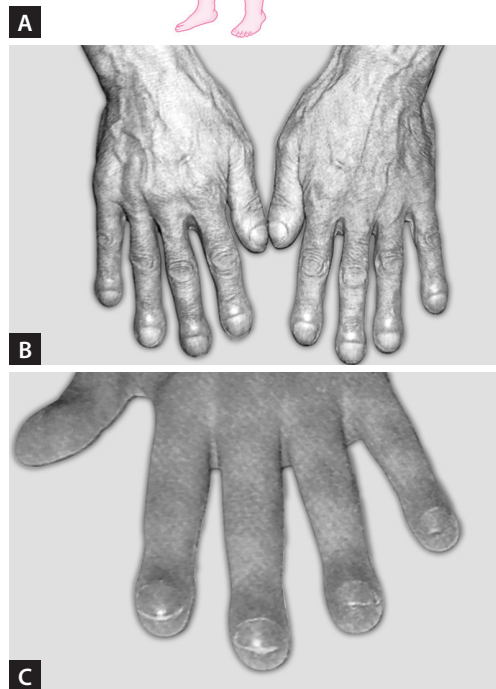
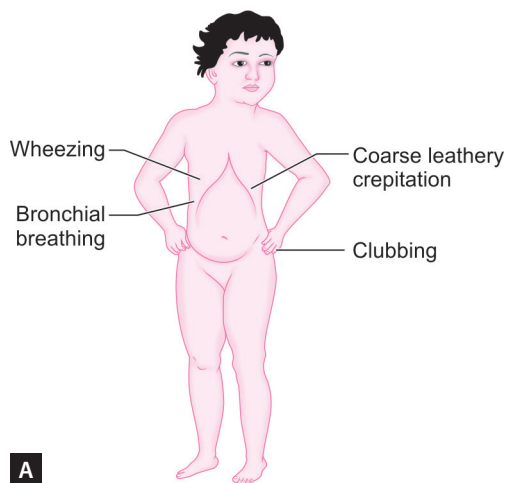
Child will typically have chronic cough, with purulent sputum, fever and weight loss. Sputum is copious mucopurulent. Onset of the disease is insidious. Bouts of cough is precipitated by change in posture and waking up from supine posture. This is because of irritation of infected secretions draining into the fresh areas of lung. In the course of illness, the sputum may become blood streaked or even frank hemoptysis may occur.

### ESSENTIAL DIAGNOSTIC POINTS

- Chronic productive cough
- Recurrent respiratory infections
- Sputum is copious mucopurulent
- Clubbing of fingers
- Moist and musical rales may be heard
- Decreased air entry
- *Pulmonary function tests*: Obstructive pattern

Recurrent respiratory tract infection is common. Segmental wheezing is present in infants and young children. During acute exacerbation, hemoptysis may be present. This will vary in severity from blood-streaked sputum to exsanguinous hemorrhage. This follows intermittent improvement and relapsing course. Moist and musical rales may be heard or elicited by cough. Rales, rhonchi, decreased air entry are often heard over the bronchiectatic area.

In chronic cases, anorexia, irritability and poor weight gain is common. Clubbing of the fingers may be present. Fever is less common.



**Figs. 1A to C:** (A) Clinical features; (B and C) Clubbing of fingers.

### GENERAL FEATURES

- Cough
- Foul smelling sputum
- Recurrent respiratory tract infection
- Hemoptysis
- Anorexia
- Poor weight gain
- Chest pain

## Primary Ciliary Dyskinesia

Bronchiectasis is also the end result of primary ciliary dyskinesia (PCD). Also autosomal recessive,



PCD has a prevalence of 1 in 15,000 to 30,000, although this prevalence likely is underestimated because individuals with this disease are undiagnosed. Kartagener syndrome is the triad of bronchiectasis, sinusitis, and situs inversus. The underlying defect in PCD is an abnormal ciliary ultrastructure and function. Normally, the cilia that line the upper and lower airways have a synchronous beat that sweeps mucus from distal to proximal airways where the mucus that has foreign material can be expectorated or swallowed. In PCD, the cilia demonstrates an abnormal beating pattern or no motility at all, leading to stasis of mucus secretions. Retained mucus leads to upper and lower respiratory tract infections, and left unchecked, these infections can cause significant damage. In the lower airways, recurrent and chronic infections can lead to bronchiectasis.

## DIAGNOSIS

The aims of evaluating children with suspected bronchiectasis are:

- To confirm the diagnosis
- To define the distribution and severity of airway involvement
- To characterize extrapulmonary organ involvement associated with bronchiectasis (e.g., cor pulmonale)
- To identify familial and treatable underlying causes of bronchiectasis

The evaluation includes a complete medical history and physical examination, as well as laboratory testing, radiographic imaging and pulmonary function test.

A complete medical history, including past medical, family, travel and environmental history, is a crucial part of the evaluation and can be helpful in identifying the underlying cause for bronchiectasis. Certain features of the history should raise concern for specific underlying disorders (e.g., history of choking suggests foreign body aspiration; chronic aspiration should be considered in patients with recurrent pneumonia particularly those with neurologic dysfunction).

The general physical examination of the patient with suspected bronchiectasis may also identify the features described above that point to an underlying etiology, including failure to thrive, sinus and ear infections, neurologic dysfunction, and the presence of congenital anomalies. In addition, the pulmonary examination may reveal the following features: crackles and rhonchi, which are often heard over the area of bronchiectasis;

wheezing, which is less common; clubbing of the nail bed, which is a basic clinical sign of bronchiectasis; and chest wall deformity, which can be seen in obstructive lung diseases [e.g., cystic fibrosis], in which hyperinflation of the lungs results in increased anterior in posterior chest diameter.

On evaluation chest radiograph, findings that are suspicious for bronchiectasis include recurrent/persistent infiltrates or atelectasis in the same lobe or segment. Ciliary dyskinesia should be considered in patients with recurrent sinus and ear infections, and evaluated with a nasal mucosal biopsy. Potential mechanisms of aspiration should be assessed using videofluoroscopy, esophageal pH monitoring, and/or nuclear scintigraphy. For patients with focal bronchiectasis, imaging and/or bronchoscopy should be performed to assess for airway obstruction (e.g., airway foreign body or congenital pulmonary anomalies). Pulmonary function tests can be helpful to evaluate the severity of lung disease and should be performed in older children. Most patients with bronchiectasis have features of obstructive lung disease, indicated by low forced expiratory volume in one second (FEV<sub>1</sub>) and FEV<sub>1</sub>/forced vital capacity (FVC) ratio.

White blood cell count is often increased with polymorphonuclear leukocytosis. Erythrocyte sedimentation rate (ESR) is raised.

X-ray criteria suggesting of bronchiectasis:

- Ring-like densities with clear centers. This suggests thick walled bronchi
- Rail road tract
- Bronchial lumen plugged with mucopurulent material is seen as white-rounded densities
- Ill-defined irregular vascular markings
- Honeycomb appearance indicating multiple small abscess cavities in later stages

Bronchography is useful for the diagnosis. Flexible bronchoscopy combined with instillation of contrast is safe and more convenient procedure. The findings are air fluid levels in distended bronchi, linear array or cluster of cysts, thick bronchial walls and dilated peripheral bronchi.

Bronchoscopy is useful in diagnosis and management of bronchiectasis. It is used to exclude bronchial stenosis due to stricture, tumor or foreign body in a suspected and proven case of bronchiectasis. It is useful in collecting material for staining and culture. It helps in localizing segment or lobe for contributing massive secretion or bleeding. It helps to remove the mucus plug.

Bronchial diameter is never larger than accompanying blood vessels. If it is found, it is an early indicator of bronchiectasis—signet ring sign.

#### LABORATORY SALIENT FINDINGS

- Chest radiograph
- Flexible bronchoscopy
- CT scan helps in grading localizing and in follow-up of the progress of disease
- Tuberculin test
- Sputum examination

High resolution CT scan with the smaller sections is performed. It is replaced bronchography. It is useful in detecting early disease, grading and localizing and in follow-up of the progress of disease.

Sputum should be sent for culture and sensitivity. The most common bacteria detected in cultures from lower respiratory tract include *S. pneumoniae*, *S. aureus*, nontypical *H. influenzae*, and *P. aeruginosa*. Nontuberculous mycobacterial species may also be detected. Tuberculin test is done to rule out tuberculosis.

Pilocarpine iontophoresis is done for estimating sweat chloride in patients with suspected cystic fibrosis.

The diagnosis of PCD can be difficult to establish. Certainly, nasal congestion is a symptom of PCD that can occur in all individuals, but in the child who has nasal congestion from birth, PCD should be considered. Most notably, patients with PCD will have a year-round, wet cough starting in infancy. Other factors that would alert the clinician to the diagnosis of PCD are neonatal respiratory distress, wheeze, bronchiectasis, and recurrent sinusitis and otitis media. Nonrespiratory issues that would raise suspicion of PCD include situs inversus or other heterotaxy syndromes, complex congenital heart disease, ectopic pregnancies, and male infertility.

The most important factor in diagnosing PCD is considering the diagnosis, after which screening and diagnostic tests help establish a diagnosis. Diagnosis requires phenotypic features of disease and a combination of variables depending on age because not all ciliary defects result in abnormal findings on all tests. In children older than 5 years of age who are capable of performing lung function testing, nasal nitric oxide can be measured.

#### DIFFERENTIAL DIAGNOSIS

Differential diagnosis include sinusitis, tuberculosis, asthma, ciliary dyskinesia, cystic fibrosis, respiratory allergy, immunodeficiency status,

surfactant deficiencies, and collagen vascular diseases. Foreign body aspiration and allergic bronchopulmonary aspergillosis should also be considered.

#### TREATMENT

During acute exacerbations, bacterial infections should be controlled and airway is kept clear of secretions. Postural drainage with pulmonary physiotherapist may be useful.

There are two phases in the management of bronchiectasis:

1. *Immediate phase:* This includes the correction of factors damaging the lung. Antibiotics, chest physiotherapy and gravitational drainage are the components of this phase. Acute infection is the indication for antibiotics. Bronchoscopy is useful in this phase to remove the foreign body, to collect the material for investigation and to remove the mucus plug. Drug treatment includes antibiotics such as penicillin, aminoglycosides and metronidazole to be given for 3 weeks till sputum decreases and symptoms subside.
2. *Long-term or surgical plan:* In acute phase, surgery is not indicated. It is advisable to delay surgery till the extent of disease is defined. Management should be aggressive in localized disease to prevent the spread of the disease to other parts of normal lung tissue. Surgical removal of an area lung affected with severe bronchiectasis is considered when the response to medical treatment is poor. Other indications include severe localized or unilateral disease, repeated hemoptysis and recurrent pneumonia in one area. Surgical treatment is reserved for localized. It is reserved till complication force the surgical intervention in bilateral disease. Extrinsic compression of bronchi requires surgical intervention.

Much of the treatment of PCD has been adopted from experience with cystic fibrosis, Enhancing mucociliary clearance with chest physiotherapy and monitoring and treating acute exacerbations with antibiotics remain the mainstay of treatment. As with cystic fibrosis, individuals with PCD can become infected with organisms such as *S. aureus*, *H. influenzae*, and *P. aeruginosa*. Intense monitoring and treatment such as identifying and treating infections are important to stabilizing lung function. Inhaled medications

such as bronchodilators, hypertonic saline, and mucolytics have been used to aid in mucus clearance and are recommended on a case-by-case basis. Genetic counseling should also be offered to parents of an affected child or those who are carriers of known disease-causing mutations. Preoperatively all children should be screened by pulmonary function tests to confirm enough lung reserves, so that removal of diseased lung tissue will be tolerated. Endobronchial tuberculosis is ruled out by bronchoscopy. If endobronchial tuberculosis is present, it should be treated adequately before the surgery is undertaken.

*Advantages of surgical treatment* includes prevention of disease to nonaffected lung disease, improves the quality of work.

*Contraindication of surgery* includes diffuse bronchitis, emphysema or pulmonary or cardiac insufficiency.

## PREVENTION

All lung infections should be treated adequately till chest is clear of all signs, long after the fever has subsided. Measles and whooping cough, should be prevented by specific immunization.

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## PRESENTING COMPLAINTS

A 4 months old boy was brought with the complaints of:

- Cold since 3 days
- Cough since 3 days
- Fever since 2 days
- Breathlessness since 4 hours

## History of Presenting Complaints

A 4-month-old boy with the history of sudden onset of breathlessness has been brought to the hospital by the mother. There was history of fever. Child had been suffering from the cold for 3 days. But there was no history of nasal block. Later child developed dry and irritating cough. This was associated with subcostal recession, intercostal indrawing. There was history of the disturbed sleep and difficulty in taking feeds.

## Past History of the Patient

Child was born at full-term by normal delivery. Child cried immediately after the delivery.

### CASE AT A GLANCE

#### Basic Findings

Length	: 62 cm (75th centile)
Weight	: 5.5 kg (50th centile)
Temperature	: 39°C
Pulse rate	: 126 per minute
Respiratory rate	: 56 per minute
Blood pressure	: 50/40 mm Hg

#### Positive Findings

##### History

- Cold
- Cough
- Breathlessness
- Fever

##### Examination

- Irritable
- Intercostal recession
- Wheezing
- Hepatomegaly

##### Investigation

- Chest X-ray: Hyperinflation with patchy shadows

The birth weight was 3 kg. There was no significant postnatal event except for the normal physiological jaundice. Breastfeeding was given immediately. He had attained neck control and there was social smile. He was completely immunized.

He was the second sibling of the nonconsanguineous marriage. The elder sister of the boy had similar problem and was admitted in the hospital.

## EXAMINATION

On examination, child was well-built and nourished. He was crying, irritable and dyspneic. The anthropometric measurements included. The length of child was 62 cm (75th centile), the weight of the child was 5.5 kg (50th centile), and the head circumference was 40 cm.

The child was febrile. The pulse was 126 per minute, the respiratory rate was 56 per minute, and the blood pressure recorded was 50/40 mm Hg. Subcostal recession and intercostal drawings were present.

There was no pallor, no lymphadenopathy, cyanosis and no edema. Respiratory system revealed the presence of fine crackles audible towards the end of the inspiration, especially at the base of the lung. Per abdomen examination revealed mild distension and presence of nontender hepatomegaly. Cardiovascular system was normal except for tachycardia.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 8,600 cells/cu mm
DLC	: P <sub>65</sub> L <sub>25</sub> E <sub>5</sub> B <sub>2</sub>
ESR	: 20 mm in the 1st hour
X-ray chest	: Hyperinflation with small patchy shadows

## DISCUSSION

A 4-month-old child was presented with the history of cough and breathlessness and it was associated

with irritability and intercostal indrawing. These findings along with hyperinflated chest radiograph lead to the diagnosis of bronchiolitis. Bronchiolitis is clinical syndrome characterized by coughing, tachypnea, labored breathing, and hypoxia.

Bronchiolitis is a common disease of lower respiratory tract. It occurs as a result of inflammatory obstruction of bronchioles. It occurs commonly in the first 2 years of life. The peak incidence occurs approximately at 6 months of age.

Several risk factors are present. They are male infants, age between 1 and 6 months, bottle fed babies, crowded place upper respiratory infection and parental smoking.

Besides young age (<6 months) at the start of the respiratory syncytial viral (RSV) season, epidemiologic studies have identified select groups of infants at high risk for severe disease and mortality including premature birth, compromised cardiopulmonary function [chronic lung disease or congenital heart disease (CHD)], trisomy 21, or immunocompromise. Males with severe RSV and lower respiratory tract infections (LRTIs) outnumber females by 1.6 to 1. Risk factors such as low socioeconomic status and modifiable risk factors such as exposure to second have also been associated with an increased risk for more severe RSV disease.

Humans are the only known reservoir for RSV. Studies of transmission dynamics suggest that infection of infants often follows infection of older siblings. The incubation period ranges from 2 to 8 days, most commonly 4–6 days. In infants hospitalized with primary RSV infection, continuous viral shedding for 10 or 11 days detected by polymerase chain reaction (PCR) is commonly observed; young infants and immunocompromised children may shed the virus for 3–4 weeks.

Transmission primarily occurs by inoculation of nasopharyngeal or ocular mucous membranes after direct contact with contaminated secretions or fomites. RSV can persist for 30 minutes or more on hands and for several hours on environmental surfaces. Close adherence to infection control policies is critical to limit healthcare-associated transmission.

Other viruses responsible are parainfluenza virus (type 3), rhinovirus, adenovirus, influenza type A, and *Mycoplasma pneumoniae*. Dual infection with RSV and human metapneumovirus is associated with severe bronchiolitis. The source of infection is family member with respiratory

disease. It is responsible for provoking wheezing at all age.

It can be classified into three types for practical purposes—acute, subacute and chronic type. On the pathogenetic basis it can be classified into two types—inflammatory and suppurative. Bronchiolitis obliterans is a classic example of inflammatory type of bronchiolitis.

## PATHOGENESIS

Respiratory syncytial viral infection is first established in the upper respiratory tract by infecting the ciliated cells of the nasopharynx, paranasal sinuses, or Eustachian tubes of the inner ear. One to 3 days later, 30% of infants who experience their first infection will demonstrate involvement of the lower respiratory tract. In the lower respiratory tract, RSV infects the small bronchial epithelium, spreading to the type 1 and type 2 alveolar pneumocytes. RSV infection is restricted to the respiratory epithelium and rarely spreads outside the respiratory tract. Disseminated disease has been documented in patients with T-cell deficiency. Infants are more likely to develop severe distal airway disease, because of an immature immune system, the lack of full protection from maternal antibodies, and also the smaller bronchiolar lumen of infants compared with older children and adults. In addition, in infants, collateral ventilation in alveolar regions is not well developed; thus, the impact of obstruction resulting from infection and inflammation is greater.

Bronchiolitis, which refers to inflammation of smaller intrapulmonary airways, is the single most distinctive clinical syndrome of RSV infection. The RSV is the causative agent in 50% cases. RSV belongs to the genus *Pneumovirus* within the *Paramyxoviridae* family: It is an enveloped, single-stranded, negative-sense RNA virus with a diameter spanning 100–350 nm. The viral envelope is studded with spike-like projections that include the fusion (F) and attachment (G) surface glycoproteins, but unlike most paramyxoviruses, RSV surface-proteins lack both hemagglutinin (HA) and neuraminidase (NA) activity. The G protein initiates the infection, while the F glycoprotein mediates viral penetration by fusing viral and cellular membranes, contributing to syncytia formation. These 2 proteins carry the antigenic determinants that elicit the production of neutralizing antibodies by the host. Human RSV exists as 2 antigenic subgroups, A and B,

which can cocirculate during the same season and exhibit genome-wide sequence divergence.

Histopathologically, airway plugging with mucus, necrosis of the bronchial and bronchiolar epithelium, and peribronchial inflammation with mononuclear cell predominance has been noted. The peribronchial infiltrate may extend into the adjacent pulmonary interstitium. Cytoplasmic inclusion bodies have been described, but syncytia formation is uncommon. Neutrophils are found between small airways and vascular structures and represent the predominant cell type in the bronchoalveolar lavage of RSV-infected infants.

Bronchiolar obstruction occurs. This is because of edema and accumulation of mucus and cellular debris. This can also be because of invasion of smaller radicals of bronchial tree by the virus. This produces bronchial spasm. The bronchial lumen is reduced.

There is marked increase in the airway resistance and reduction in airflow. Resistance to airflow is increased both during inspiration and expiration. The radius of the airway is smaller during expiration. Hence, the bronchioles are partially collapsed. The egress of the air is severely restricted during this phase. This leads to the trapping of air inside the alveoli. This produces emphysematous changes. This occurs as a result of ball valve respiratory obstruction leading to early air trapping and over inflation. When the obstruction becomes complete the trapped air in the lungs may be absorbed causing atelectasis.

This leads to ventilation perfusion mismatch. This mismatch will lead to hypoxia. Carbon dioxide retention occurs leading to respiratory failure. Hyperpnea is usually not found until the respiratory rate exceeds 60 per minute.

The immunopathogenesis is advocated. Bronchiolitis is less severe in RSV vaccinated babies. Protection against is mediated by antibodies to IgG 3 subclass. These antibodies have shorter half-life and do not cross the placenta in substantial amount so as to give protection to infant. High quantities of secretory IgA antibodies to RSV are present in the colostrum and breastfeeding reduces the likelihood of hospitalization with bronchiolitis. RSV bronchiolitis leads to the IgE synthesis. These IgE responders release chemical mediators such as histamine, leukotriene  $C_4$ , etc. These produce smooth muscle constriction. Some may develop into asthma later in life. The presence of eosinophils in the blood and respiratory secretions suggest virus infection initiates the wheezing attack in child who is already sensitized.

## CLINICAL FEATURES (FIG. 1)

Respiratory syncytial viral infection is heralded by initial symptoms indistinguishable from those of the common cold. The infant may show rhinitis and cough, and there may be fever. Within 1–2 days, the cough becomes more prominent and tachypnea may develop. At first there will be rhinorrhea and sneezing. Rhinorrhea is serous nasal discharge. There will be family history of upper respiratory tract infection in family member. Cough may be very mild and may be associated with wheeze. These symptoms may last for several days. These may be accompanied by diminished appetite and fever. In mild cases, the symptoms disappear by 1–3 days.

With increasing respiratory effort, substernal and intercostal retractions are noted along with nasal flaring and abdominal breathing. In more severely affected infants, symptoms may develop within several hours and course is protracted. The respiratory distress will develop. This is characterized by paroxysmal wheeze, cough, dyspnea and irritability. Feeding difficulty associated with increasing dyspnea will be present grunting can be present in more severe cases. The expiratory phase is prolonged, and the chest is hyperexpanded and hyper-resonant, providing further evidence of generalized expiratory airflow obstruction. Those with severe disease may develop retraction lower intercostal spaces and suprasternal notch by 3–5 days.

Apnea can be an early manifestation of RSV infection in young infants, particularly infants <8 weeks old or those with a history of premature birth or apnea of prematurity. Apnea can occur associated, with respiratory tract symptoms or may be the only sign at presentation. Recurrent apnea is a serious complication. Few children will have vomiting and diarrhea.

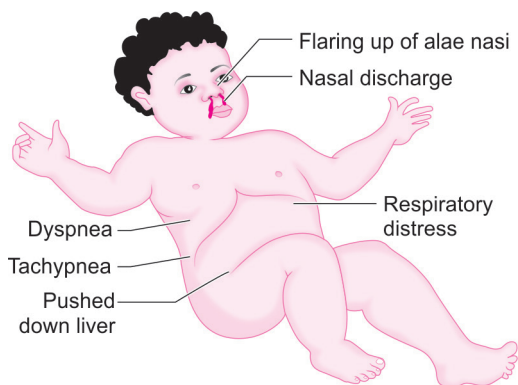


Fig. 1: Clinical features.

On examination, there is varied respiratory rate. Tachypnea is usually present. There is flaring up of alae nasi, use of accessory muscles resulting in intercostal and subcostal retraction. These are shallow because of persistence distension of lungs by the trapped air. Liver and spleen are palpable, being pushed down by over or hyperinflated lungs. On auscultation, crackles or rales with or without diffuse expiratory wheezing are usually heard. Widespread crackles may be heard at the end of inspiration and in early expiration. Wheeze are audible when the expiratory phase of the breathing is prolonged. In children requiring hospitalization, hypoxemia is typical, reflecting ventilation-perfusion mismatch.

The most critical phase of the illness occurs during 48–72 hours after the onset of cough and dyspnea. Apneic spell occurs. Respiratory acidosis occurs. Periodic breathing may also occur. Hypoxic episodes will also occur. Cyanosis, apnea and bradycardia are common.

The characteristic findings on examination are:

- Sharp dry cough
- Tachypnea
- Subcostal and intercostal recession
- Fine end-inspiratory crackles
- Hyperinflation chest
- High pitched wheezes
- Tachycardia
- Cyanosis, pallor.

Cardiac failure is overdiagnosed. This is because of pushed down liver secondary to over inflation of lungs. It rarely occurs in the absence of underlying cardiac disease. Over distension of one lung, i.e., Macleod syndrome sometimes occurs.

The cause of death is prolonged apneic spells, severe uncompensated respiratory acidosis and profound dehydration occurs due to loss of water from tachypnea, irritability to drink water. Mortality rate is high with congenital heart disease, bronchopulmonary dysplasia and immunodeficiency diseases.

#### GENERAL FEATURES

- Mild upper respiratory tract infection
- Sneezing
- Cough
- Irritability

#### ESSENTIAL DIAGNOSTIC POINTS

- Acute onset of cough rhinorrhea.
- Tachypnea and expiratory wheezing.
- Nasal flaring shallow rapid respirations.
- RSV is the most common pathogen.
- Apneic spell, respiratory acidosis, periodic breathing.

## DIFFERENTIAL DIAGNOSIS

**Bronchial asthma:** Bronchiolitis is often confused with bronchial asthma. The latter is unusual below the age of 1 year; a family history of asthma is usually present. Several attacks occur in the same patient with or without a preceding respiratory infection. Response to bronchodilators is more consistent in children with asthma as compared to bronchiolitis.

**Congestive heart failure:** Congestive heart failure is suggested, if there is cardiomegaly on X-ray film of chest, tachycardia, large tender liver, raised JVP, edema and rales on auscultation of the lungs.

**Foreign bodies in trachea:** These are diagnosed by the history of aspiration of foreign body, localized wheeze and signs of collapse or localized obstructive emphysema.

**Bacterial pneumonia:** In bacterial pneumonia, the signs of obstruction are less pronounced, fever is high and adventitious sounds in the lungs are prominent.

## DIAGNOSIS

Bronchiolitis is a clinical diagnosis; however, other respiratory viruses also cause bronchiolitis in young children, and clinical features are insufficient to reliably distinguish RSV from these other viral infections. Specific viral diagnosis may be helpful in certain scenarios: when the diagnosis is uncertain; to reduce unnecessary use of antibiotics; or in hospitalized children at risk for severe disease or for infection control purposes. Detection of RSV from nasopharyngeal specimens may be achieved by rapid antigen tests including fluorescence-based methods such as direct fluorescent antibody (DFA: sensitivity 90–95%, specificity 92–97%) or immunoassays such as enzyme immunoassay (EIA: sensitivity 80%, specificity 75–100%). Detection by viral culture or by serology is not clinically practical for early diagnosis of acute RSV infection. Serology also is challenging to interpret in young infants because of the presence of maternal antibodies.

In cell culture, RSV growth is detected within 5–7 days by the typical plaque morphology with syncytium formation. Cell culture was traditionally the gold standard for diagnosis, but this technique has been replaced by the more rapid and sensitive rt-PCR assays. rt-PCR is the most sensitive method for RSV detection and allows the differentiation between A and B subgroups (which is useful for surveillance purposes in cases of respiratory disease outbreaks). Studies have shown that

approximately 30% of children hospitalized with RSV bronchiolitis may be co-infected with another respiratory virus. Whether children with RSV bronchiolitis who are co-infected with another respiratory virus develop more severe disease is still unclear.

Respiratory viruses are now identified by PCR analysis of nasopharyngeal secretions. Nasopharyngeal secretion should be aspirated and sent for immunofluorescence, enzyme linked immunosorbent assay (ELISA). This test will be positive for RSV in winter epidemics, occasionally adenoviral infection especially 3, 7 and 21 serotypes.

The chest X-ray need not be done routinely and is indicated only in children with severe respiratory distress or when there is diagnostic dilemma. The radiographic findings of bronchiolitis include hyperinflation, patchy infiltrates that are typically migratory and attributable to postobstructive atelectasis, and peribronchial cuffing. Because bronchiolitis is not a disease of the alveolar spaces, a secondary bacterial pneumonitis should be suspected if a true alveolar infiltrate is seen on chest radiograph. Diaphragm is pushed down.

Pulse oximetry is used to measure and monitor arterial oxygen saturation. Blood gas analysis usually capillary sample is performed in severe disease to identify hypercarbia when additional ventilator support is considered.

#### LABORATORY SALIENT FINDINGS

- Radiograph of chest shows overinflation.
- Nasopharyngeal secretion should be aspirated and sent for immunofluorescence, enzyme linked immunosorbent assay (ELISA).
- ABG shows respiratory acidosis.
- Viral culture.
- Leukocytosis.

## TREATMENT

Child should be hospitalized. The child should be placed in humid atmosphere. Child may not take feed properly because of tachypnea. Hence, nasogastric tube feeding is advised. Intravenous fluid is indicated if the child is not tolerating oral feeds.

Currently, the primary treatment for RSV infection is supportive and includes nasal suctioning, hydration. In hospitalized patients close cardiorespiratory monitoring and measurement of oxygen saturation. Nasal suctioning may provide relief of upper airway obstruction, but deep suctioning of the nasopharynx is not recommended. Although infants with bronchiolitis are at risk of developing-subsegmental atelectasis,

chest physiotherapy has not been shown to be of clinical benefit. Humidified oxygen is frequently required when managing hospitalized infants since hypoxemia is common (oxygen saturation <90%) in more severe illness.

Humidified oxygen is given to relieve hypoxemia and reduce the insensible water loss due to tachypnea. This will relieve dyspnea and cyanosis. Very sick infants require a concentration of 70% through the hood. Assisted ventilation in the form of nasal or facemask CPAP or full ventilation is required in some admitted infants.

Pulse oximeter should be used to monitor oxygen saturation more than 95%. The infant will be more comfortable at 30–40° angle or with head and chest elevated.

The complications associated with hypoxemia and carbon dioxide (CO<sub>2</sub>) retention generally begin when the respiratory rate surpasses 60 breaths per minute. Admission to pediatric intensive care units and use of noninvasive or invasive ventilatory support because of severe respiratory distress, hypoxemia, or apnea are required in 10–20% of children hospitalized with RSV bronchiolitis.

#### Indications for hospitalization:

- Moderate to severe dehydration
- Retraction apnea
- Poor feeding
- Cyanosis
- SaO<sub>2</sub> < 91%
- RR > 70/min
- Marked respiratory distress with retraction
- Younger than 6 months

Inhaled bronchodilators, such as albuterol or racemic epinephrine, or inhaled or systemic corticosteroids are not recommended for the management of children with RSV bronchiolitis. Nebulized hypertonic saline has been shown to increase mucociliary clearance and may be beneficial in infants who are expected to have prolonged hospitalizations (>72 hours). Last, except for acute otitis media, bacterial infections of the lower respiratory tract are rarely associated with RSV infection; thus, antibiotic treatment is usually not indicated for LRTI.

Wheezing and rhonchi are usually present. Hence it is very difficult to differentiate from first attack of asthma. Trial of bronchodilator salbutamol is given. Bronchodilator may be continued round the clock if there is improvement clinically.

There is improvement in lung function with the high dose 0.5 mg/kg nebulized epinephrine. This will reduce the mucosal edema. This is by alpha receptor stimulation. This produces



constriction of precapillary arterioles reducing microvascular leakage.

Antibiotics are indicated in the presence of fever, clinical deterioration, high WBC count, raised CRP and infiltration on chest X-rays.

Ribavirin is an antiviral agent. It is given by aerosol 16 hours a day for 3–5 days. It shortens the course of illness in infants with underlying congenital heart disease, chronic lung disease and immunodeficiency.

Ribavirin is indicated

- High risk severe or complicated RSV infection
- RSV infection with lower respiratory tract infection who are seriously ill
- Mechanically ventilated infants

Ribavirin is a broad-spectrum virostatic antiviral agent with activity against RSV and other RNA viruses. Early on, small, double-blinded, placebo-controlled studies showed a beneficial effect in infants treated with aerosolized ribavirin soon after onset of disease. The required aerosol route of administration, concerns about potential toxic effects among exposed healthcare personnel, possible teratogenicity in pregnant women, conflicting results of efficacy trials, and high cost have led to infrequent use of ribavirin.

Beta-2-adrenergic drugs and ipratropium are used in infants above 6 months. If patient improvement, bronchodilators may be given every 4–6 hourly. Continuous positive airway pressure (CPAP) or assisted ventilation may be required to control respiratory failure. Extracorporeal membrane oxygenation is effective, if respiratory failure is not controlled by mechanical ventilation.

## PROGNOSIS

Most of them recover from acute infection within 2 weeks. Fifty percent will have recurrent episodes cough and wheeze. Rarely with infection adenovirus illness may result in permanent damage of airways—bronchiolitis obliterans. Bronchiolitis due to RSV infection contributes to morbidity and morbidity in children with underlying medical disorder, including chronic disease of prematurity, CF, congenital heart disease and immunodeficiency. Death may occur in one percent of severely ill patients due to respiratory failure. The relationship to bronchial asthma is 25% of cases of bronchiolitis.

## PREVENTION

Monoclonal antibody to RSV (palivizumab) is given monthly by intramuscular injection, reduces number of hospitalization in high preterm babies.

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## PRESENTING COMPLAINTS

A 20-month-old boy was brought with the complaints of:

- Cold, cough since 2 days
- Fever since 1 day
- Noisy breathing since 4 hours
- Difficulty in breathing since 4 hours

## History of Presenting Complaints

A 20-month-old boy with the sudden onset of harsh brassy cough was brought to the hospital at about 3 AM in the morning. The cough was associated with noisy breathing. The child was irritable and uncomfortable. He was breathless. He was not able to take any feeds. He had common cold 2 days back and had been treated with medicines. The boy had high temperature. There was also history of difficulty in swallowing.

### CASE AT A GLANCE

#### Basic Findings

Height	: 82 cm (75th centile)
Weight	: 11 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 120 per minute
Respiratory rate	: 64 per minute
Blood pressure	: 60/40 mm Hg

#### Positive Findings

##### History

- Sudden onset of brassy cough
- Noisy breathing
- Cold 2 days back
- Breathlessness

##### Examination

- Irritable
- Stridor
- Rhonchi, crepitation
- Breathlessness
- Breath sounds diminished

##### Investigation

- Chest X-ray: Steeple sign
- ABG: Features of hypoxia

## Past History of the Patient

He was the only sibling of the nonconsanguineous marriage. He was born at full term with the normal delivery. His birth weight was 2.8 kg. There were no significant postnatal events. The child was breastfed for 6 months. Weaning started at the age of 4 months and child was taking all the family food by the age of 1 year. His developmental milestones were normal. He had been completely immunized.

## EXAMINATION

The child was well built and nourished. The child was irritable and dyspneic. Noisy, brassy cough was present. Anthropometric measurements include, the height was 82 cm (75th centile), and the weight was 11 kg (50th centile).

The child was febrile. Heart rate was 120 per minute. The respiratory rate was 64 per minute. Intercostal indrawing was present. Subcostal recession was present. Blood pressure recorded was 60/40 mm Hg. Central cyanosis was present. There was no pallor, no icterus, no clubbing, and no lymphadenopathy.

The respiratory system revealed the inspiratory stridor. The noisy breathing was conducted and heard all over the chest. Breath sounds were diminished. Rhonchi and aspiration are present. There was occasional expiratory stridor. Per abdomen examination revealed mild distension. No organomegaly. Cardiovascular system revealed the presence of tachycardia.

## INVESTIGATION

Hemoglobin	: 14 g/dL
DLC	: P <sub>80</sub> L <sub>15</sub> M <sub>1</sub> E <sub>2</sub> B <sub>1</sub>
ESR	: 20 mm in 1st hour
Chest X-ray	: Subglottic narrowing, i.e., steeple sign
Serum electrolytes	: Na : 130 mEq/L K : 5 mEq/L Cl : 90 mEq/L

Arterial blood gas analysis : pH < 7  
 $\text{PaO}_2$  : 60 mm Hg  
 $\text{PaCO}_2$  : 40 mm Hg  
 $\text{HCO}_3$  : 20 mEq/L

## DISCUSSION

The presenting symptoms and physical examination point to diagnosis of acute laryngotracheobronchitis, i.e., croup. The croup is mainly caused by viruses. These include parainfluenza, adenovirus, respiratory syncytial virus, influenza and measles viruses. Sometimes bacterial infection occurs secondarily. The bacteria responsible are *M. pneumoniae*, *Haemophilus influenzae*, group A streptococci, pneumococci and staphylococci.

Croup describes acute inflammatory diseases of the larynx-laryngitis, spasmodic laryngitis, including viral croup (laryngotracheobronchitis), epiglottitis (supraglottitis), and bacterial tracheitis.

There is mucosal inflammation and increased secretions affecting the airway, but it is the edema of subglottic area that is potentially dangerous in young children because it may result in critical narrowing of the trachea.

The airway resistance is inversely proportional to the 4th power of radius. Hence, any mucosal edema in the small airways leads to significant increase in the work of breathing, narrowing and may lead to respiratory difficulty. Infection of these parts of the respiratory tract produces a dry hacking cough and hoarseness of the voice giving them a common name of croup syndrome. There are four clinically distinct syndrome. These include acute laryngitis, laryngotracheobronchitis, spasmodic laryngitis, and acute epiglottitis.

## CLINICAL FEATURES (FIG. 1)

Croup is the most common cause of the acute respiratory tract infection leading to obstruction. Most of them have upper respiratory infection before cough becomes apparent. At first, there will be only mild brassy cough with intermittent respiratory stridor. As obstruction increases, the stridor becomes obvious. It is associated with nasal flaring, suprasternal, infrasternal and intercostal retraction.

Viral croup occurs between 6 and 36 months of age, but the peak incidence is in the 2nd year of life. Usually illness begins with rhinorrhea and within to 12–24 hours, a barking cough and stridor develop. The stridor is usually prominent during inspiration. Fever is variable finding. The degree of airway obstruction varies from maximum to severe.

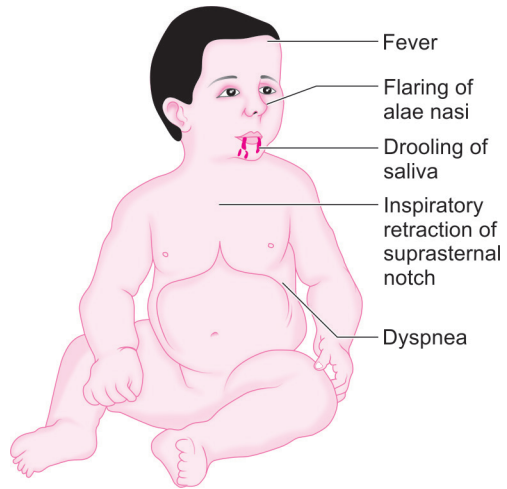


Fig. 1: Clinical features.

The symptoms often start, and are worse in the night.

Sometimes there may be fulminating course of fever, sore throat, dyspnea, rapidly progressing obstruction, and prostration. Sometimes aphonia and drooling of saliva are noted. Dysphagia is also common.

The primary findings include inflammatory edema, distribution of ciliated epithelium, and exudates. As the inflammation exceeds the bronchi and bronchioles, respiratory difficulty occurs. Expiratory phase of the respiration becomes labored and prolonged. Later air hunger and restlessness occur. There will be stridor, and increasing pulse rate and deaths may occur from hypoventilation. In the hypoxic child, who may be cyanotic, pale and obtunded, any manipulation of the pharynx may result in cardiorespiratory arrest. Subglottic edema will be associated with inflammation of trachea and bronchi (laryngotracheobronchitis) is common.

With the further compromise of the airway, air hunger and restlessness occur. These are superseded by severe hypoxemia, hypercapnia and weakness. These are accompanied by decreased air exchange and stridor tachycardia and eventual death from hypoventilation.

Physical examination reveals inspiratory and expiratory stridor, flaring up of alae nasi, and inspiratory retraction of the suprasternal notch. There will be diminished breath sounds, rhonchi, and scattered crackles.

The child may assume tripod position sitting upright and leaning forward with the chin up and mouth open while bending the arm.



**ESSENTIAL DIAGNOSTIC POINTS**

- Acute inflammatory disease of larynx including viral croup and bacterial tracheitis
- There will be stridor, and increasing pulse rate and deaths may occur from hypoventilation
- Fulminating course of fever, sore throat, dyspnea, rapidly progressing obstruction and prostration
- Nasal flaring, suprasternal, infrasternal and intercostal retraction
- Subglottic edema will be associated with inflammation of trachea and bronchi

**GENERAL FEATURES**

- Mild brassy cough
- Stridor
- Air hunger
- Restlessness
- Sore throat
- Aphonia
- Hypoxemia and weakness

**DIAGNOSIS**

Croup is a clinical diagnosis and does not require any investigation. Radiographs are used only if diagnosis is uncertain. The X-ray of the neck may show the typical subglottic narrowing or steeple sign on the posteroanterior (PA) view. However, the steeple sign may be absent in patients with croup. Radiograph does not reflect the severity of airway obstruction.

Neck anteroposterior radiograph shows narrowing of subglottic portion of the trachea producing inverted V (steeple sign), without irregularities seen in tracheitis.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis includes conditions that cause obstruction in the region of larynx:

- *Epiglottitis*: It is very rare in India.
- *Laryngeal foreign body*: Sudden onset of choking and coughing without prodromal signs of infection.
- *Acute angioedema*: Usually presents with swelling of the face and neck and other manifestations of allergic reactions.
- *Retropharyngeal and peritonsillar abscess*: A peritonsillar abscess is often a clinical diagnosis whereas radiograph or computed tomography (CT) scan of upper airway helps in diagnosis of retropharyngeal abscess.
- *Bacterial tracheitis*: Although, it is very rare, it is important differential diagnosis as it may have fulminant course and needs antibiotic.
- *Laryngeal diphtheria*: Early symptoms of diphtheria include malaise, sore throat,

anorexia, and low-grade fever. Within 2–3 days a typical gray-white membrane on tonsils and/or soft palate is seen on pharyngeal examination. Fine membrane is adherent to the tissue, and forcible attempts to remove it cause bleeding.

- *Measles croup*: It always has full manifestations of systemic disease and the course may be fulminant.
- *Bronchial asthma*: A croupy cough may be an early sign of asthma.
- *Subglottic stenosis*: It presents from early infancy and is not associated with prodromal symptoms.

**COMPLICATIONS**

Complications include bronchopneumonia, cervical lymphadenitis, otitis media, meningitis, septic arthritis, tracheobronchitis and pneumothorax.

**TREATMENT**

The mainstay of treatment for children of croup is airway management.

*Indications for hospitalization* include actual or suspected epiglottitis, progressive stridor, severe stridor at rest, respiratory distress, hypoxemic restlessness, cyanosis, pallor, depressed sensorium, and high fever in toxic appearing child. Fluid should be administered for adequate hydration of the patient by intravenous route.

**BASIC MANAGEMENT**

- Do not examine the throat
- Observe signs of hypoxia or deterioration
- If severe, administer nebulized adrenaline
- Urgent tracheal intubation, if respiratory failure develops

Therapy includes primarily maintaining and providing adequate respiratory exchange. Use of steam often terminates laryngeal spasm and respiratory distress within minutes.

The inspired air is cooler than the body temperature and less than 100% saturated with water vapor results in mucosal cooling, leading to the vasoconstriction and lessened edema.

Frequent continuous monitoring of the respiratory rate is essential as rapid and rising respiratory rate may be the first sign of hypoxia and fatal respiratory obstruction.

Oxygen should be used to alleviate hypoxemia and apprehension. Persistence of the

cyanosis in spite of giving oxygen is an indication for tracheostomy. These patients should be observed closely.

Unnecessary manipulation of the patient may induce laryngeal spasm. After the laryngeal spasm released, its return may be prevented by the use of warm or cool humidification near the child's bed for 2–3 days. The patient should be disturbed as minimal as possible.

Parenteral intravenous fluid is given to make up the insensible and respiratory water loss. This decreases the risk of vomiting if given as oral feed. Hence, risk of aspiration is taken care. Sedatives are not indicated as the resistance by the child is main indicator of distress.

Racemic epinephrine is given by nebulizer (0.5 mL of 2.25% solution diluted in sterile saline) is commonly used solution in the doses of 2–4 mL for 15 minutes. This has rapid onset of action within 10–30 minutes. It will give transient relief. Close observation and repeated treatment is usually necessary.

The use of corticosteroid is indicated to reduce the inflammatory edema and to prevent the obstruction of the ciliated epithelium. Dexamethasone in the dose of 0.6 mg/kg/day is used. Single intramuscular injection of dexamethasone reduces disease severity in first 24 hours with decreased need of intubation and adrenaline nebulization. The topical nonabsorbed inhaled corticosteroid for the treatment is budesonide.

The dose is 2–4 mg. Beneficial effect of inhalation budesonide is seen. Inhalation of budesonide in dose of 2–4 mg twice a day for 2 days is useful. Oral dexamethasone (0.15 mg/kg) may be equally effective for mild to moderate croup. Heliox, a mixture of (80% helium, 20% oxygen mixture) is used to decrease the respiratory difficulty.

Antibiotics such as ampicillin 100 mg/kg/day or chloramphenicol 50 mg/kg/day are used. A single daily dose of ceftriaxone may be used. Rifampicin prophylaxis for unimmunized children below 2 years should be considered.

In patients with impending respiratory failure an airway must be established. Intubation with an endotracheal tube of slightly smaller diameter than would ordinarily be used is reasonably safe. Extubation should be accomplished within 2–3 days to minimize risk of laryngeal injury. If patient fails extubation, tracheostomy may require.

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## PRESENTING COMPLAINTS

A 7-year-old boy was presented with the complaints of:

- Fever since 1 week
- Cough since 1 week
- Generalized weakness since 1 week
- Chest pain since 2 days
- Vomiting since 2 days

## History of Presenting Complaints

A 7-year-old boy was brought to the emergency room with the high grade fever, cough and with generalized weakness. Fever of moderate to high degree was present since 1 week. Fever was continuous type, sometimes associated with chill.

Fever used to be relieved to some extent by antipyretics. The child had productive cough. He was bringing out the sputum. Sputum was yellowish or white in color. Child used to have disturbed sleep because of the cough. There was associated history of the pain in the chest on the left side. Pain was increasing on taking deep inspiration. Child had vomiting since 2 days. He was not tolerating any food.

## Past History of the Patient

He was the first child of the nonconsanguineous marriage. He was born at full term by normal delivery. There was no significant postnatal event. The birth weight of the child was 3 kg. He was given breast milk. His developmental milestones were normal. His performance at school was good. There was no previous history of measles, tuberculosis and whooping cough. There was no family history of similar complaints. There was no family history of tuberculosis.

### CASE AT A GLANCE

#### Basic Findings

Height	: 120 cm (75th centile)
Weight	: 20 kg (30th centile)
Temperature	: 40°C
Pulse rate	: 120 per minute
Respiratory rate	: 22 per minute
Blood pressure	: 100/70 mm Hg

#### Positive Findings

##### History

- Cough
- Fever
- Chest pain
- Vomiting

##### Examination

- Toxic
- Dehydrated
- Tenderness over the chest
- Clubbing
- Tracheal shift
- Diminished breath sounds
- Stony dullness

##### Investigation

- *TLC*: Increased
- *DLC*: Neutrophilia
- *ESR*: Raised
- *X-ray chest*: Homogeneous opacity
- *Thoracocentesis*: Pus had no organism

## EXAMINATION

The boy was moderately built and poorly nourished. He was looking much toxic. There were signs of moderate dehydration. His height was 120 cm (75th centile), and the weight was 20 kg (30th centile). He was febrile, i.e., 40°C. Pulse rate was 120 per minute. The respiratory rate was 22 per minute. The blood pressure recorded was 100/70 mm Hg.

There was pallor, clubbing was present. There was no lymphadenopathy. Tenderness was present over the left inframammary region. Bony tenderness was present. Trachea was shifted to the right side. Stony dullness was present on percussion. Chest movements were diminished on left side. Breath sounds were diminished. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 9.8 g/dL
TLC	: 22,000 cells/cu mm

DLC	: $P_{78} L_{18} E_2 M_2$
ESR	: 40 mm in the 1st hour
X-ray chest	: Presence of homogeneous opacity on the left side
Thoracentesis	: Gram staining of the pus showed no organism
Pus culture and sensitivity	: Sterile

## DISCUSSION

The child had high degree fever, respiratory distress and signs of moderate dehydration. Productive cough is associated with foul smelling sputum and presence of clubbing are suggestive of suppurative lung disease. Tenderness at the chest, tender clubbing and toxic look suggest empyema. Pus on thoracentesis confirms the diagnosis.

## PATHOPHYSIOLOGY

Empyema means collection of thick pus in pleural cavity. It occurs in children below 5 years. Certain organisms are common among certain age groups. Most common organism is *S. pneumoniae*. *Staphylococcus aureus* is common in children less than 2 years of age. *Haemophilus influenzae* type B are common in children up to 5 years. *Pneumococcus* may also occur in this age. Group A *Streptococcus* and *Pneumococcus* are common in older children and adolescents. *Pseudomonas aeruginosa* is suspected in immunocompromised, debilitated, hospitalized parents. It is commonly caused as complication of staphylococcal (rarely *S. pneumoniae* or gram negative bacilli) pneumonia or rupture of subdiaphragmatic or liver abscess in pleura.

Empyema results from the rupture of lung abscess, trauma, intra-abdominal abscess, septicemia, meningitis, malignancies. These are often loculated due to thickened pleura, fibrous septae and inadequate drainage. They can be synpneumonic, when associated with pneumonia or metapneumonic when they occur after pneumonia.

Empyema necessitans is the term used when the pus dissents through the chest wall and produces a superficial swelling in subcutaneous tissue under the skin. Empyema along with bronchopleural fistula indicates chronicity of disease process, fibrosis. This is associated with tuberculosis empyema.

Thickening of the parietal pleura occurs if pus is not drained. It may dissect through pleural space into the lung parenchyma. This produces bronchopleural fistula and pyopneumothorax or into the abdominal cavity. Pockets of loculated

pus may eventually develop into the thick-walled abscess cavity.

There are three stages of development of the empyema. It is important to know the phases of development. This will help to plan the treatment and also for the prognosis.

1. *Exudative phase*: It is an immediate response with the accumulation of their fluid with low cellular content. This stage lasts for few hours to few days. This stage responds well to the appropriate antibiotic. It requires intercostal drain placement. This may be adequate.
2. *Fibrin purulent phase*: There will be collection of pus. This contains many polymorphonuclear cell and fibrin. This lasts for about 2–10 days. It is ideally treated with decortication.
3. *Organizing phase*: There will be formation of “peel”. This is due to the growth of fibroblast on pleural surface. It leads to the chronic loss of lung function. With the increasing fibrous, intercostal space decreases leading to rib crowding and scoliosis. Open thoracotomy is the treatment of choice.

### ESSENTIAL DIAGNOSTIC POINTS

- Appear toxic and have greater respiratory difficulty
- High fever, cough and breathlessness
- Tenderness at the chest, tender clubbing and toxic look
- Pus on thoracentesis
- Bronchopleural fistula indicates chronicity of disease process, fibrosis

## CLINICAL FEATURES (FIG. 1)

The initial signs and symptoms are those of bacterial pneumonia. The most of the cases are febrile. There will be acute history of high fever, cough and breathlessness. They often appear toxic and have greater respiratory difficulty. In critical condition the patient may be cyanosed. There will be stony dull note on chest percussion, absent air entry on affected side, and tenderness with the tracheal and mediastinal shift.

### GENERAL FEATURES

- Toxic look
- Signs of dehydration
- Leukocytosis
- Increased erythrocyte sedimentation rate (ESR)

Older children or those with chronic empyema may not look so ill. Child will show the signs of hydropneumothorax if bronchopleural fistula develops. Clubbing may develop. Empyema necessitans should be thought if child develops a superficial chest wall swelling.

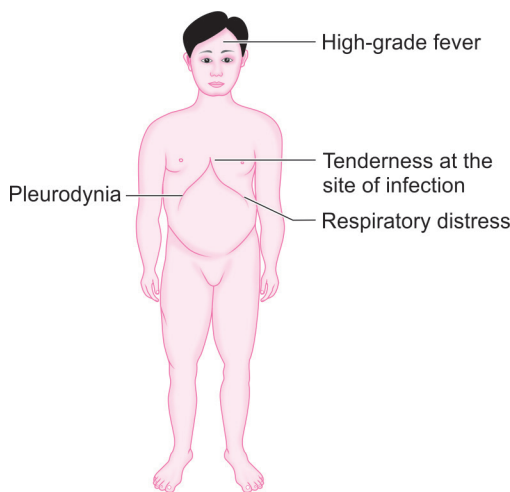


Fig. 1: Clinical features.

## DIAGNOSIS

Increased white blood cell count, polymorphonuclear leukocytosis and raised ESR support the diagnosis.

### Chest X-ray

A standard posteroanterior (PA) view of the plain X-ray is relatively insensitive to detect pleural effusion. In general, a minimum of 400 mL of pleural fluid should be required to detect by upright chest X-ray. Decubitus films may detect as little as 50 mL of fluid. A density of more than 10 mm suggests sufficient volume for tapping.

In a child with worsening pneumonia, a repeat X-ray should be advised. In the presence of empyema, it will show the presence of fluid. Failure of fluid to shift on X-ray in various positions indicates loculation. They also demonstrate subpulmonic effusion.

In cases with underlying bronchopleural fistula, air fluid level will be present. Loculation is seen with organization phase. Crowding of ribs with scoliosis suggests chronic empyema.

There will be obliteration of cardiophrenic angle, fluid level in pyopneumothorax and collapsed lung tracheal and mediastinal shift is obvious.

Significant scoliosis on chest X-ray and evidence of parenchymal entrapment are indications for prolonged hospital course and suggests surgical intervention.

### Diagnostic Thoracocentesis

It helps in distinguishing between parapneumonic effusion and empyema. Fluid collected should be

examined for Gram stain in anaerobic and aerobic cultures, pH measurement, measurement of glucose and lactate dehydrogenase (LDH).

Pus that is aspirated shows opaque fluid, polymorphs in abundance, protein content more than 3 g/dL and pleural fluid. Serum protein concentration is more, pleural LDH levels more than 200 and pleural LDH ratio greater than 0.6 are diagnostic of exudates. Pus with polymorph indicates empyema. Pleural biopsy may also help in arriving at diagnosis and etiology.

Empyema severe score includes: (a) pleural fluid pH < 7.2, (b) pleural fluid glucose level < 40 mg%, and (c) presence of anaerobic infection.

### Chest Ultrasound

It is a very useful tool for diagnosis, guidance of thoracocentesis, or pleural catheter placement. It is especially helpful when the radiograph shows a white out. Sonography can distinguish solid from liquid pleural abnormalities with much higher accuracy compared to skiagrams. Sonography gives valuable information regarding size of effusion, presence of adhesions or loculations and the echogenicity of the pleural fluid. Sonographic appearance of pleural fluid varies according to the stage of effusion; ranging from an anechoic completely echo-free or sonolucent parapneumonic effusion to very echogenic fluid with septa as seen in frank empyema. Ultrasonography shows limiting membranes suggesting the presence of loculated collections even when they are not so well seen on computed tomography (CT) scan.

It may detect smaller amount of fluid. It helps to differentiate pleural thickening from effusion. It helps in locating pleural fluid, amount of fluid, presence of loculation and to know about the condition of the underlying lung, i.e., presence of consolidation in the underlying lobe.

It will evaluate nature of fluid. Pleural fluid may be transudate or exudate. Multiple echogenic foci indicate thick exudate or empyema. It differentiates lung and pleural pathology. It is useful as prognostic indicator.

### CT Scan

Empyema appears well-defined, smooth, round or elliptical on CT scan. The parietal and visceral layers are separated by interposed empyema fluid, giving rise to "split pleura sign" of empyema. CT scans should not be performed routinely as it exposes the child to a very high radiation dose while most information for diagnosis and for

guiding treatment decisions can be received from a good sonogram. It may have a limited role in the cases which do not respond to the initial medical management or before surgery to delineate the anatomy and to rule out a lung abscess.

It helps in identifying exact anatomy, amount of pus, loculation, thickness of “peel” and condition of underlying lung parenchyma. Margins separating the density from adjacent lung, bone soft tissues are well-defined. CT can be of value in distinguishing subpulmonic and subphrenic collections in patients with an elevated hemidiaphragm seen on X-ray.

#### LABORATORY SALIENT FINDINGS

- Increased white blood cell count, polymorphonuclear leukocytosis and raised ESR
- Chest X-ray
- Diagnostic thoracocentesis
- Chest ultrasound
- CT scan

It is useful in differentiating pleural from parenchymal disease. This distinction is important because antibiotic therapy and postural drainage are appropriate for lung abscess, whereas thoracotomy, tube drainage is important for empyema.

## TREATMENT

### Choice of Antibiotics

It depends upon the Gram stain and culture and sensitivity. However, most of these patients are on antibiotics, the culture may not be much useful.

When the organism is not identifiable, ampicillin with cloxacillin and cloxacillin with third generation cephalosporin is the right combination.

Staphylococcal empyema is best treated with penicillin or vancomycin, or cloxacillin. Pneumococcal infection is treated by penicillin or cefotaxime. *H. influenzae* responds to cefuroxime, cefotaxime, ceftriaxone and azithromycin.

Systemic antibiotic therapy is required for at least 2–3 weeks.

### Intercostal Drainage

Pus is drained immediately and controlled by an underwater seal or continuous suction. A large

bore intercostal drainage is inserted into the site where the accumulation of pus is suspected. It should achieve dependent drainage. It may achieve adequate drainage in exudates phase especially in the single cavity without loculation. However, it fails to achieve adequate drainage once loculation develops. Chest tubes that are no longer draining should be removed. Fibrinolytic enzymes or proteolytic enzymes are instilled into the pleural cavity. Systemic antibiotic therapy is required.

### Decortication

It is the surgical procedure. It involves the removal of fibrinous tissue from the parietal or visceral pleura to release lung entrapment.

In patients, who remain afebrile and dyspneic longer than 72 hours of initiation of therapy with intravenous antibiotics and intercostal drainage, surgical decortication are indicated. Surgical treatment is advised if pneumatoceles produce respiratory distress.

Now with the better understanding of pathophysiology of empyema formation, once the loculi are formed, intercostal drainage will fail to resolve empyema completely. Hence on detection of empyema, if the loculation have already started developing, the patient should be subjected to primary decortication even prior to intercostal drainage.

Advantages of early decortication include decreased length of duration of intercostal drainage and good success rate with primary treatment modality.

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## PRESENTING COMPLAINTS

A 20-month-old boy was brought with complaints of:

- Cough and cold for 3 days
- Excessive crying for 1 day
- Discharge in right ear for 1 day

## History of Presenting Complaints

A 20-month-old baby was brought to the pediatric outpatient department with the history of discharge in the right ear. Mother noticed the ear discharge in the morning. Mother gave the history of excessive crying of the child and irritability of the child in the night. Mother could not make out the reason for crying. She administered the paracetamol syrup and cough syrup as prescribed by the general practitioner for cough, cold and fever. She revealed that her baby had cough and cold for which she had sought family doctor's advice.

### CASE AT A GLANCE

#### Basic Findings

Height	: 82 cm (75th centile)
Weight	: 11 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 120 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 60/40 mm Hg

#### Positive Findings

##### History

- Pain in the ear
- Discharge in the right ear
- Cough, cold, fever
- Excessive crying

##### Examination

- Febrile
- Features of rhinitis
- Nasal block
- Otoscopic examination—perforation in the right ear

##### Investigation

- TLC—increased
  - Polymorph leukocytosis

## Past History of the Patient

He was the only sibling of the nonconsanguineous marriage. He was born at full-term with normal vaginal delivery. His birth weight was 3 kg. There was no significant postnatal event. The child was exclusively on breast milk for 6 months. Weaning started at the age of 4 months. Child was taking all the family food by the age of 1 year. His developmental milestones were normal. He had been completely immunized.

## EXAMINATION

Child was well built and nourished. The child was irritable and was not ready to lie on the examination table. Anthropometric measurements included the height 82 cm (75th centile) and weight was 11 kg (50th centile).

The child was febrile. Heart rate was 120 per minute. The respiratory rate was 26 per minute. Blood pressure recorded was 60/40 mm Hg. The ear discharge was present in the right ear. Left ear was normal. There was no pallor, no icterus, no clubbing and no lymphadenopathy.

Features suggestive of rhinitis, i.e., nasal discharge, nasal block were present. Throat was congested. Otoscopic examination revealed the presence of perforation in tympanic membrane. All the systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 14 g/dL
Total count	: 12,800 cells/cu mm
DLC	: P <sub>80</sub> L <sub>15</sub> M <sub>1</sub> E <sub>2</sub> B <sub>1</sub>
Erythrocyte sedimentation rate	: 20 mm in the 1st hour
Ear discharge for culture and sensitivity	: Sterile
Otoscopic examination	: Perforation in the tympanic membrane Right side

## DISCUSSION

The child had the upper respiratory infection associated with cough, cold and fever. Child was irritable, was crying a lot and later mother noticed the discharge in the ear. Along with the otoscopic findings the diagnosis of otitis media was done.

Otitis media (inflammation of the middle ear) is an infection associated with middle ear effusion (a collection of fluid in the middle ear space) or otorrhea (a discharge from the ear through a perforation in the tympanic membrane or ventilating tube).

Otitis media can be further classified by its associated clinical symptoms, otoscopic findings, duration, frequency, and complications. The more specific classifications are acute otitis media, otitis media with effusion (residual or persistent effusion), and chronic suppurative otitis media.

### Acute Otitis Media

Acute otitis media (AOM) is commonly defined as inflammation of the middle ear resulting in an effusion and associated with rapid onset of symptoms such as otalgia, fever, irritability, anorexia, or vomiting. An ear effusion is best documented by pneumatic otoscopy or tympanometry.

### Otitis Media with Effusion

Otitis media with effusion is defined as an asymptomatic middle ear effusion that often follows AOM, but may have no such antecedent history. Otoscopic findings that suggest otitis media with effusion (OME) include visualization of air-fluid level or bubbles, and a clear or amber middle ear fluid. Effusion is usually associated with either a mild or moderate conductive hearing impairment of 15 dB or higher. OME can also be associated with negative middle ear pressure, which results in prominence of the malleus and a negative pressure peak on tympanometry.

To distinguish AOM from otitis media with effusion, signs of inflammation of the tympanic membrane (TM) or symptoms of acute infection must be present. Otoscopic findings specific for AOM are a bulging TM; impaired visibility of the ossicular landmarks; a yellow, white, or bright red color; opacification of the eardrum; and exudates or bullae on the eardrum.

### Pathophysiology and Predisposing Factors

Eustachian tube dysfunction (ETD)—The Eustachian tube regulates middle ear pressure and allows for drainage of the middle ear. It must

periodically open to prevent the development of negative pressure and effusion in the middle ear space. If this does not occur, negative pressure leads to transudation of cellular fluid into the middle ear, as well as influx of fluids and pathogens from the nasopharynx and adenoids. Middle ear fluid may then become infected, resulting in AOM. The Eustachian tube of infants and young children is more prone to dysfunction because it is shorter, more compliant, and more horizontal than in adults. The Eustachian tube reaches its adult configuration by the age of 7 years. Infants with craniofacial disorders, such as Down syndrome or cleft palate, may be particularly susceptible to ETD.

Bacterial colonization—nasopharyngeal colonization with *S. pneumoniae*, *Hemophilus influenzae*, or *Moraxella catarrhalis* increases the risk of AOM, whereas colonization with normal flora such as viridans streptococci may prevent AOM by inhibiting growth of these pathogens.

Viral upper respiratory infections—upper respiratory infections (URIs) increase colonization of the nasopharynx with otitis pathogens. They impair Eustachian tube function by causing adenoid hypertrophy and edema of the Eustachian tube itself. It is not absolutely clear if viral pathogens are the primary cause of episodes of AOM or if they help promote bacterial infections.

Passive smoking increases the risk of persistent middle ear effusion (MEE) by enhancing colonization, prolonging the inflammatory response, and impeding drainage of the middle ear through the Eustachian.

Impaired host immune defenses—immunocompromised children such as those with selective immunoglobulin A (IgA) deficiency usually experience recurrent AOM, rhinosinusitis, and pneumonia. However, most children who experience recurrent or persistent otitis only have selective impairments of immune defenses against specific otitis pathogens.

Bottle feeding—breastfeeding reduces the incidence of acute respiratory infections, provides IgA antibodies that reduce colonization with otitis pathogens, and decreases the aspiration of contaminated secretions into the middle ear space which can occur when a bottle is propped in the crib.

Season—the incidence of AOM correlates with the activity of respiratory viruses, accounting for the annual surge in otitis media cases during the winter months in temperate climates.

Genetic susceptibility—although AOM is known to be multifactorial, and no gene for



susceptibility has yet been identified, recent studies of twins and triplets suggest that as much as 70% of the risk is genetically determined.

Age—children ages 1–3 years are at greatest risk for AOM.

### Microbiology of Acute Otitis Media

**Bacterial pathogens:** The three most common bacterial otopathogens are *S. pneumoniae*, nontypeable *H. influenzae*, and *M. catarrhalis*. Less common bacteria include *Streptococcus pyogenes* (group A), which causes 29–10% of AOM, tends to occur in older children, and is more frequently associated with TM perforation and mastoiditis. Rare pathogens detected in the MEE include *Chlamydia*, *Mycoplasma*, *Mycobacterium tuberculosis*, and fungi.

**Viral upper respiratory tract infection (URTI)** is exceedingly common in infants and children and often leads to AOM. It has been suggested that certain viruses are more likely to cause AOM than others. It is likely, however, that any virus that causes URTI is able to induce AOM. A broad spectrum of respiratory viruses causes URTI; rhinoviruses and coronaviruses are the most common among them. Other common URTI viruses are adenoviruses, respiratory syncytial virus (RSV), parainfluenza viruses, human metapneumovirus, influenza viruses, enteroviruses.

Bacterial or viral pathogens can be detected in up to 96% of middle ear fluid samples from patients with AOM. Polybacterial infections are seen in up to 55% of cases, with bacterial and viral coinfections occurring in up to 70%. *S. pneumoniae* and *H. influenzae* account for 35–40% and 30–35% of isolates, respectively. With widespread use of the pneumococcal conjugate vaccine starting in 2000, the incidence of AOM caused by *H. influenzae* rose while that of the *S. pneumoniae* vaccine serotypes declined. However, there has been an increase in disease caused by *S. pneumoniae* serotypes not covered by the vaccine as well as *S. aureus*. The third most common pathogen cited is *M. catarrhalis*, which causes up to 15–25% of AOM cases. The fourth most common organism in AOM is *Streptococcus pyogenes*, which is found more frequently in school-aged children than in infants. *S. pyogenes* and *S. pneumoniae* are the predominant causes of mastoiditis. The most common viruses associated with AOM are RSV, influenza virus, adenovirus, human metapneumovirus, and enteroviruses.

Drug-resistant *S. pneumoniae* is a common pathogen in AOM and strains may be resistant to

only one drug class (e.g., penicillins or macrolides) or to multiple classes. Children with resistant strains tend to be younger and to have had more unresponsive infections. Antibiotic treatment in the preceding 3 months also increases the risk of harboring resistant pathogens.

### CLINICAL FEATURES (FIG. 1)

Symptoms of AOM are generally nonspecific, including fever, irritability, restless sleep, decreased appetite, vomiting, and diarrhea. Fever occurs in one-third to two-thirds of children with AOM, but temperatures of 40°C or more are unusual unless accompanied by invasive bacterial disease or foci elsewhere. Because AOM most often occurs during URTI, there are also symptoms such as cough, sneezing, runny nose, stuffy nose, and red/watery eyes. Purulent conjunctivitis has been associated with AOM due to nontypeable *H. influenzae*.

Ear pain may manifest as ear tugging in infants. In children 6 months to 3 years of age with URTI, ear tugging does not differentiate children with URTI and AOM from those with only URTI. Earache is not universal in AOM; about one-fifth of children older than age 2 do not complain of ear pain. The ear pain is due to pressure of the increasing suppuration in the middle ear and is relieved when the pressure leads to ischemia of the central vessels in the capillary bed of the TM. Persistent ischemia leads to necrosis of the TM with rupture and discharge of the contents of the middle ear abscess and virtual elimination of the otalgia. Parents often report that a child who had cried with pain was relieved and bloody pus

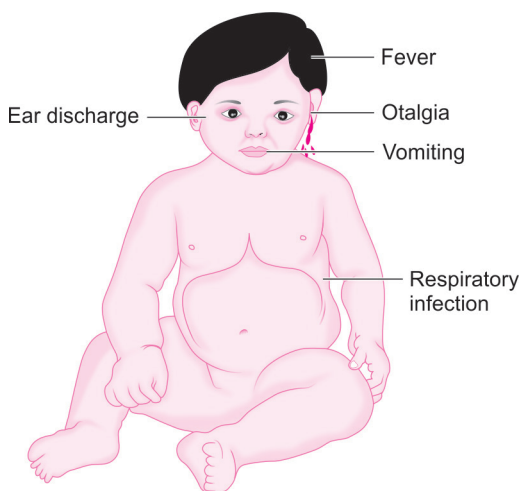


Fig. 1: Clinical features.

was observed. However, the TM is so vascular that the site of perforation may not be evident even 24 hours later, and the resealed membrane may result in reaccumulation of the purulent MEE.

Hearing loss is a frequent sign in infants. It may be expressed by verbal children or detected by a parent who sees the child not responding to spoken voice.

## DIAGNOSIS

Otologic examination should include evaluation of the position, color, and degree of translucency and mobility of the TM. The normal eardrum should be in the neutral position. Mild retraction of the TM usually indicates the presence of negative middle ear pressure, an effusion, or both. Severe retraction of the TM identifies high negative pressure associated with MEE. Fullness or bulging of the TM is caused by increased middle ear pressure or MEE.

The normal TM has a ground-glass appearance and is translucent. The otoscopist should be able to look through the TM and visualize the middle ear landmarks. A blue or yellow color identifies MEE seen through a translucent TM. A red TM may indicate inflammation but may also identify engorgement of the blood vessels of the TM caused by crying, sneezing, or nose-blowing. Adequate examination of the TM to confirm the MEE is sometimes difficult, particularly in infants and small children.

The diagnosis of AOM generally requires: (1) abrupt onset of symptoms; (2) presence of MEE (bulging of the TM, limited or absent mobility of the TM, or otorrhea); and (3) signs or symptoms of middle ear inflammation. As AOM develops, there is a spectrum of signs seen during the progression of TM inflammation and MEE accumulation.

The guideline requires bulging TM as evidence for middle ear inflammation. Three degrees of bulging are defined: mild, moderate, and severe. For mild bulging of the TM, intense erythema must also be present. The Indian Academy of Pediatrics (IAP) guideline has tightened the AOM working definition, in order to differentiate AOM from OME, recognizing that the AOM definition likely results in high specificity but less sensitivity as it may exclude less severe presentations of AOM.

Pneumatic otoscopy is the most feasible and cost-effective method for diagnosis of AOM and OME. Mobility of the TM is identified by pressure applied to the rubber bulb attached to the pneumatic otoscope. The normal or air-filled

middle ear is identified by a brisk movement inward with slight positive pressure and outward with slight negative pressure. MEE or high negative pressure within the middle ear dampens movement of the TM. Movement of the TM is best seen in the posterosuperior quadrant of the TM.

Tympanometry and acoustic reflectometry can supplement pneumatic otoscopy. Tympanometry involves varying the pressure in the external canal accompanied by a probe tone. A graphic presentation, the tympanogram, provides information on middle ear pressure and the presence of an air-filled or fluid-filled middle ear space. Because tympanometry and pneumatic otoscopy require a seal in the external canal for a few seconds, they may be difficult to perform in the young infant who is irritable due to ear pain.

### ESSENTIAL DIAGNOSTIC POINTS

- Otitis media (inflammation of the middle ear) is an infection.
- Associated with middle ear effusion (collection of fluid in the middle ear space).
- Otorrhea (a discharge from the ear through a perforation in the tympanic membrane).
- Otalgia, fever, irritability, anorexia, or vomiting.
- Otoscopic findings specific for AOM are a bulging TM; impaired visibility of the ossicular landmarks.

### GENERAL FEATURES

- Irritability
- Anorexia
- Inflammation of tympanic membrane
- Perforation of tympanic membrane

## COMPLICATIONS

Untreated acute otitis media may occasionally cause serious extracranial or intracranial complications. *Extracranial complications* include acute mastoiditis, subperiosteal and neck abscesses, and facial palsy. *Intracranial complications* may include meningitis or intracranial abscess. Fortunately, such complications are now less common due to increased availability of antibiotics.

### Tympanosclerosis, Retraction Pockets, Adhesive Otitis

Tympanosclerosis is an acquired disorder of calcification and scarring of the TM and middle ear structures from inflammation. If tympanosclerosis involves the ossicles, conductive hearing loss may result. The term myringosclerosis applies to calcification of the TM only and is a fairly common sequela of OME and AOM. Myringosclerosis may

also develop at the site of a previous tympanostomy tube; tympanosclerosis is not a common sequela of tube placement.

### Cholesteatoma

A greasy-looking mass or pearly white mass seen in a retraction pocket or perforation suggests a cholesteatoma. If infection is superimposed, serous or purulent drainage will be seen, and the middle ear cavity may contain granulation tissue or even polyps. Persistent, recurrent, or foul-smelling otorrhea following appropriate medical management should make one suspect a cholesteatoma.

### Tympanic Membrane Perforation

Occasionally, episode of AOM may result in rupture of the TM. Discharge from the ear is seen and often there is rapid relief of pain. Perforations due to AOM usually heal spontaneously within a couple of weeks. Otological antibiotics are recommended for a 10–14 days course and patients should be referred to an otolaryngologist 2–3 weeks after the rupture for examination and hearing evaluation.

When perforations fail to heal, surgical repair may be needed. TM repair is generally delayed until the child is older and Eustachian tube function has improved. Repair of the eardrum (tympanoplasty) is generally deferred until around 9 years of age, which is approximately when the Eustachian tube reaches adult orientation. In otherwise healthy children, some surgeons perform a repair earlier if the contralateral, nonperforated ear remains free of infection and effusion for 1 year.

### Facial Nerve Paralysis (Fig. 2)

The facial nerve traverses the middle ear as it courses through the temporal bone to its exit at the



Fig. 2: Facial palsy.

stylomastoid foramen. Normally the facial nerve is completely encased in bone, but occasionally bony dehiscence in the middle ear is present, exposing the nerve to infection and making it susceptible to inflammation during an episode of AOM. The acute onset of a facial nerve paralysis should not be deemed idiopathic Bell palsy until all other causes have been excluded. If middle ear fluid is present, prompt myringotomy and tube placement are indicated. CT is indicated if a cholesteatoma or mastoiditis is suspected.

### Chronic Suppurative Otitis Media

This type of otitis media is defined as persistent otorrhea lasting longer than 6 weeks. Most often it occurs in children with tympanostomy tubes or TM perforations. Occasionally, it is an accompanying sign of cholesteatoma.

Chronic suppurative otitis media (CSOM) is present when persistent otorrhea occurs in a child with tympanostomy tubes or TM perforation, it starts with an acute infection that becomes chronic with mucosal edema, ulceration, granulation tissue, and eventual polyp formation, risk factors include a history of multiple episodes of otitis media, living in crowded conditions, day care attendance and being a member of a large family. The most common associated bacteria include *P. aeruginosa*, *S. aureus*, *Proteus* species, *Klebsiella pneumoniae*, and diphtheroids. Visualization of the TM, meticulous cleaning with culture of the drainage, and appropriate antimicrobial therapy, usually topical, are the keys to management.

### Labyrinthitis

Suppurative infections of the middle ear can spread into the membranous labyrinth of the inner ear. Symptoms include vertigo, hearing loss, and fevers. The child often appears extremely toxic. Intravenous antibiotic therapy is used, and intravenous steroids may also be used to help decrease inflammation. Sequelae can be serious, including a condition known as labyrinthitis ossificans, or bony obliteration of the inner ear, including the cochlea, leading to profound hearing loss.

### Acute Mastoiditis

The spread of infection into the mastoid bone results in acute mastoiditis. Differential diagnosis must include a severe case of otitis externa, as both processes may present with swelling and

tenderness of the ear canal, periaural region and mastoid process.

A CT scan will show clouding or coalescence of the air cells in acute mastoiditis and may be necessary to differentiate the two conditions. Untreated, this may progress to an abscess within the confines of the mastoid cells or spread externally, leading to the formation of subperiosteal or deep neck abscesses.

Acute mastoiditis should initially be treated with parenteral antibiotics directed against the aforementioned pathogens, adding coverage for gram-negative and anerobic organisms only if mastoiditis is superimposed upon a history of a chronically discharging ear, where colonization with such bacteria is common.

Surgery in the form of a cortical mastoidectomy is reserved for cases with poor response to parenteral antibiotic therapy, subperiosteal abscess, an intracranial complication or acute mastoiditis in a chronic ear.

#### TREATMENT OF ACUTE OTITIS MEDIA

##### First-line therapy

1. Amoxicillin 90 mg/kg/day, up to 2 g daily. For children over 2 years or age, give for 5 days; under 2 years of age, for 10 days.
2. If amoxicillin has caused a rash, give cefuroxime (Ceftin) or cefdinir (Omnicef)
3. If urticaria or other IgE-mediated events have occurred, give trimethoprim-sulfa or azithromycin (zithromax)
4. If the child is unable to take oral medication, give single intramuscular dose of ceftriaxone (Rocephin).

##### Second-line therapy

This is for clinical failure after 48–72 hours of treatment, or for recurrences within 4 weeks.

1. Amoxicillin-clavulanate (Augmentin ES-600), given so that the patient receives amoxicillin at 90 mg/kg/day.
2. If amoxicillin has caused allergic symptoms, see recommendations above.

##### Third-line therapy

1. Tympanocentesis is recommended to determine the cause.
2. Ceftriaxone (Rocephin), two doses given intramuscularly, 48 hours apart, with the option of a third dose.

##### Recurrences >4 weeks after the first episode

1. A new pathogen is likely, so restart first-line therapy.
2. Be sure the diagnosis is not OM with effusion (OME), which may be observed for 3–6 months without treatment.

## TREATMENT

### The Observation Option

The choice to observe an episode of AOM and not treat with antibiotics is an option in otherwise healthy children without other underlying conditions such as cleft palate, craniofacial abnormalities, immune deficiencies, cochlear implants, or tympanostomy tubes. The decision should be made to provide antibiotic therapy if there is worsening of symptoms or lack of improvement within 48–72 hours. For infants younger than 6 months, antibiotics are always recommended on the first visit, regardless of diagnostic certainty. The clinical practice guidelines include age, presence of otorrhea, severity of symptoms, and laterality as criteria for antibiotic treatment versus observation.

Pain may be a major symptom of AOM due to pressure within the middle ear and can be substantial in the first few days of onset of illness. Antibiotic treatment does not relieve pain within the first 24 hours. Analgesics can relieve pain associated with AOM early in the course. Therefore, the child should be assessed for pain, and if pain is present, treatment for pain should be given.

Oral analgesics such as acetaminophen or ibuprofen are the mainstay of AOM pain management; they are effective for mild to moderately severe pain, narcotic analgesics with codeine or analogs may be prescribed for severe pain; risks and benefits of using these drugs, including potential toxic effects, need to be considered. Topical agents such as benzocaine or lidocaine may offer additional brief benefit over acetaminophen in children older than 5 years.

Duration of antibiotic treatment should be 10 days for children under age 2 years, while a 7-day course should be adequate for AOM in children age 2–5 years. For children age 6 years or older with nonsevere symptoms, a 5–7 days course is adequate.

As it may take 1–3 days before antibiotic therapy leads to a reduction in pain, mild-to-moderate pain should be treated with ibuprofen or acetaminophen. Severe pain should be treated with narcotics, but careful and close observation is required to address possible respiratory depression, altered mental status, gastrointestinal upset, and constipation. Topical analgesics have a very short duration and studies do not support efficacy in children younger than 5 years (**Table 1**).

**TABLE 1:** Recommendations for initial management of uncomplicated acute otitis media (AOM).

Age	Otorrhea with AOM	Unilateral or bilateral AOM with severe symptoms	Bilateral AOM without otorrhea	Unilateral AOM without otorrhea
6 months to 2 years	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation
≥2 years	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation	Antibiotic therapy or additional observation

## Antibiotic Therapy

The guideline on AOM management suggests the use of 4 factors in deciding whether to choose initial observation or prescribing antibiotics: age, severity of symptoms, presence of otorrhea, and laterality of AOM. All infants and children with severe AOM, as defined by a toxic-appearing child, persistent otalgia for more than 48 hours, or temperature of more than 39°C (102.2°F), should receive antibiotic therapy. AOM with otorrhea, presumably with rupture of the TM, also should receive antibiotic therapy. For those with nonsevere symptoms, initial observation is an option for children younger than 2 years of age with unilateral AOM. Children at least 2 years old with unilateral or bilateral AOM may also be observed initially. Initial observation without antibiotic prescription must be a shared decision with the child's family. If observation is offered, a mechanism must be in place to ensure follow-up and initiation of antibiotics if the child worsens or fails to improve within 72 hours of AOM onset.

High-dose amoxicillin is recommended as the first-line treatment because of its effectiveness against *S. pneumoniae* and *H. influenzae*, as well as its safety, low cost, acceptable taste, and narrow microbiologic spectrum. In children who have taken amoxicillin in the previous 30 days, those with concurrent conjunctivitis, and for whom coverage for beta-lactamase-positive *H. influenzae* and *M. catarrhalis* is desired, therapy should be initiated with high-dose amoxicillin-clavulanate. Treatment with an effective antibiotic results in significant resolution of acute signs and symptoms within 48–72 hours. Persistent ear pain or systemic signs, including fever after 72 hours of antibiotic therapy, indicate a need for re-evaluation for persistent AOM or foci elsewhere. If otologic findings support the diagnosis of persistent AOM, antibiotic treatment should be changed, depending on the initial drug.

Amoxicillin-clavulanate enhanced strength with 90 mg/kg/day of amoxicillin dosing (14:1 ratio of amoxicillin:clavulanate) is an appropriate choice

when a child has had amoxicillin in the last 30 days, or is clinically failing after 48–72 hours on amoxicillin.

Alternative initial antibiotics including cefuroxime and third generation cephalosporins are less efficacious than the first-line drugs. For penicillin-allergic children, cefdinir, cefuroxime, cefpodoxime, or ceftriaxone may be used as they are unlikely to be associated with cross-reactivity with penicillin; the exceptions are children with severe and/or recent penicillin allergy.

Three oral cephalosporins (Cefuroxime, cefpodoxime, and cefdinir) are more beta-lactamase-stable and are alternative choices in children who develop a popular rash with amoxicillin. Unfortunately, coverage of highly penicillin-resistant pneumococci with these agents is poor and only the intermediate-resistance classes are covered. Of these drugs, cefdinir suspension is most palatable; the other two have a bitter after taste which is difficult to conceal. Flavoring agents may be helpful here.

A second-line antibiotic is indicated when a child experiences symptomatic infection within 1st month of finishing amoxicillin; however, repeated use of high-dose amoxicillin is indicated if more than 4 weeks have passed without symptoms. Macrolides such as azithromycin and clarithromycin are not recommended as second-line agents because *S. pneumoniae* is resistant to macrolides in approximately 30% of respiratory isolates, and because virtually all strains of *H. influenzae* have an intrinsic macrolide efflux pump, which pumps the antibiotic out of the bacterial cell.

Reasons for failure to eradicate a sensitive pathogen include drug noncompliance, poor drug absorption, or vomiting of the drug. If a child remains symptomatic for longer than 3 days while taking a second-line agent, a tympanocentesis is useful to identify the causative pathogen. If a highly resistant pneumococcus is found or if tympanocentesis is not feasible, intramuscular ceftriaxone at 50 mg/kg/dose for 3 consecutive



days is recommended. If a child has experienced a severe reaction, such as anaphylaxis, to amoxicillin, cephalosporins should not be substituted. Otherwise, the risk of cross-sensitivity is less than 0.1%.

### *Management of OME*

An audiology evaluation should be performed after approximately 3 months of continuous bilateral effusion in children younger than 3 years.

Children with hearing loss or speech delay should be referred to an otolaryngologist for possible tympanostomy tube placement. Antibiotics, antihistamines, and steroids have not been shown to be useful in the treatment of OME.

Traditionally, OME was observed for 3 months in uncomplicated cases prior to consideration for tympanostomy tube placement. Longer periods of observation may be acceptable in children with normal or very mild hearing loss on audiogram, no risk factors for speech and language issues, and no structural changes to the TM. Absolute indications for tympanostomy tubes include hearing loss greater than 40 dB, TM retraction pockets, ossicular erosion, adhesive atelectasis, and cholesteatoma.

Penicillin resistance develops through stepwise mutations in the structure of the penicillin binding proteins. Strains for which minimum inhibitory concentrations (MICs) of penicillin range between 0.12–1.0/mL are said to exhibit “intermediate” resistance. Strains for which MICs are equal to or higher than 2 mL are said to have a “high level resistance.” These strains are also resistant to other drug classes.

In patients with tympanostomy tubes with uncomplicated acute otorrhea, ototopical antibiotics (fluoroquinolone ear drops) are first-line therapy. The ear drops serve two purposes: (1) They treat the infection and (2) they physically “rinse” drainage from the tube which helps prevent plugging of the tube.

### *Recurrent Otitis Media*

Recurrent AOM is defined as the occurrence of 2–3 separate, well-documented AOM episodes in a 6-month period, or 2–4 episodes in a 12-month period with at least 1 episode in the preceding 6 months. Antibiotic prophylaxis has been used to prevent recurrent AOM. Studies have shown that an estimated five children would have to be given 1 year of antibiotic prophylaxis in order to prevent 1 AOM episode. The modest benefit afforded by a prolonged course of antibiotic prophylaxis does not

have longer-lasting benefit after cessation of therapy. Because of the modest benefit and the potential adverse effects associated with prolonged antibiotic use and emergence of resistance, the AAP guideline does not recommend antibiotic prophylaxis.

The use of tympanostomy tubes is recommended for recurrent AOM. Tympanostomy tubes prevent approximately 1.5 episodes of AOM in the 6 months after surgery. The disadvantages of tube placement include the cost, surgical and anesthetic risk, and long-term sequelae such as tympanosclerosis and chronic perforation.

### **Tympanocentesis**

If a child remains symptomatic longer than 3 days while taking a second-line agent, a tympanocentesis may be needed to identify the causative pathogen. If a highly resistant pneumococcus is found or if tympanocentesis is not feasible, intramuscular ceftriaxone in 2–3 daily doses appears to be the best third-line agent. Further studies are needed in children failing second-line therapy.

Tympanocentesis is performed by placing a needle-through the TM and aspirating the middle ear fluid.

The fluid is sent for culture and sensitivity. Indications for tympanocentesis are (1) AOM in an immunocompromised patient, (2) research studies, (3) evaluation for presumed sepsis or meningitis, such as in a neonate, (4) unresponsive otitis media despite courses of two appropriate antibiotics, and (5) acute mastoiditis or other suppurative complications.

### **Surgery**

Surgical treatment, including tympanocentesis or myringotomy, results in immediate relief by draining the abscess and should be considered for the child who is toxic, who fails to improve on repeated antibiotic therapy, who has severe suppurative or nonsuppurative complications (e.g., mastoiditis or facial nerve palsy), or who has an underlying immunodeficiency. The middle ear fluid should be cultured for bacteriologic diagnosis and susceptibility testing. Presence of multidrug-resistant bacteria in the MEE may necessitate the use of antibiotics, such as levofloxacin or linezolid. Levofloxacin is a quinolone antibiotic that is not approved by the FDA for use in children. Linezolid is a relatively recent and expensive antibiotic that is effective against resistant gram-positive bacteria. Consultation with a pediatric infectious disease expert may help with selection of unconventional drugs.

## Immunologic Evaluation and Allergy Testing

While immunoglobulin subclass deficiencies may be more common in children with recurrent AOM, there is no practical immune therapy available. More serious immunodeficiencies, such as selective IgA deficiency, should be considered in children who suffer from a combination of recurrent AOM, rhinosinusitis, and pneumonia. In the school-aged child or preschooler with an atopic background, skin testing may be beneficial in identifying allergens that can predispose to AOM.

## Vaccines

The pneumococcal conjugate and influenza vaccines are recommended. The seven-valent pneumococcal conjugate vaccine (PCV7) was introduced and the 13-valent pneumococcal conjugate vaccine (PCV13). PCV7 was found to produce a 29% reduction in AOM resulting from the seven serotypes found in the vaccine, and overall, PCV7 reduced AOM by 6–7%. In recent studies, intranasal influenza vaccine reduced the number of influenza-associated cases of AOM by 30–55%.

## FOLLOW-UP VISITS

The optimal timing for follow-up visits depends on the response to therapy. Children should be

reassessed when symptoms of AOM continue beyond 72 hours or recur during treatment. The follow-up visit for preschool children should be 3–4 weeks after start of therapy.

## PROGNOSIS

Prognosis is variable based on age of presentation. Infants who are very young at the time of first otitis media are more likely to need surgical intervention. Other factors that decrease the likelihood of resolution are onset of OME in the summer or fall, history of prior tympanostomy tubes, presence of adenoids, and hearing loss greater than 30 dB.

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## PRESENTING COMPLAINTS

A 6-month-old boy was brought with the complaints of:

- Cough since 3 days
- Fever since 3 days
- Noisy respiration since 2 days
- Not taking feeds since 1 day
- Breathlessness complaints since 1 day

## History of the Presenting Complaints

A 6-month-old boy was brought to the pediatric emergency ward with the history of breathlessness and not taking feeds. The baby was accompanied by mother. There was history of fever and cough since 3 days. Fever used to be moderate to high degree. It used to get relieved by paracetamol. Cough was associated with noisy respiration and nasal block. Cough was distressed and it was disturbing the sleep as well as intake of food.

Mother has noticed mild subcostal recession and intercostals indrawing.

## Past History of the Patient

Child was born at full term by normal delivery. Child cried immediately after the delivery. The birth weight was 3 kg. There was no significant postnatal event except for normal physiological jaundice. Breastfeeding was given immediately. Weaning of the food started by 4 months. At present, he is getting breast milk and cereals. He was completely immunized.

He was the second sibling of the noncon-sanguineous marriage. The elder sibling is doing well with the health.

## EXAMINATION

On examination, the child was well built and nourished. He was crying, irritable and dyspneic. The anthropometric measurements included the length 66 cm (75th centile), the weight was 6.3 kg (50th centile) and the head circumference was 40 cm.

The child was febrile. The pulse was 136 per minute and respiratory rate was 56 per minute. The blood pressure recorded was 60/50 mm Hg. Mild subcostal recession and intercostal indrawing were present.

There was no pallor, lymphadenopathy, cyanosis and no edema. Respiratory system revealed the presence of fine crepitations at the base of the lungs. Signs of rhinitis and nasal block were present. Per abdomen examination revealed the presence of mild distension and mild nontender hepatomegaly. Cardiovascular system was normal except for tachycardia.

## INVESTIGATION

Hemoglobin : 13 g/dL  
 TLC : 14,500 cells/cu mm  
 DLC :  $P_{68} L_{25} E_5 B_2$

### CASE AT A GLANCE

#### Basic Findings

Length : 66 cm (75th centile)  
 Weight : 6.3 kg (50th centile)  
 Temperature : 39°C  
 Pulse rate : 136 per minute  
 Respiratory rate : 56 per minute  
 Blood pressure : 60/50 mm Hg

#### Positive Findings

##### History

- Cold
- Cough
- Breathlessness
- Fever
- Vomiting

##### Examination

- Irritable
- Dyspneic
- Crepitation
- Hepatomegaly

##### Investigation

- Increased WBC count
- Chest X-ray—patchy pneumonitis

ESR : 26 mm in the 1st hour  
 X-ray chest : Increased vascular marking with bilateral patchy pneumonitis

## DISCUSSION

Child was having fever, cough, cold, and breathlessness. On examination, there was fever, tachycardia, tachypnea. Respiratory system revealed the presence of crepitation at the basal of lungs. Per abdomen showed the presence of hepatomegaly. Investigation reports showed the presence of the increased white blood cell count suggests the pneumonia. Pneumonia is defined as inflammation of lung tissue may result from a noninfectious or an infectious cause.

*Bronchopneumonia* is primarily a spreading inflammation of the terminal bronchioles and their related alveoli. *Lobar pneumonia or consolidation* is a pathological state where the alveolar air has been replaced by cellular exudate and transudate.

*Pneumonitis* is localized inflammation of lung parenchyma due to noninfectious causes.

*Interstitial pneumonia* is characterized by massive proliferation and desquamation of alveolar cells and thickening of alveolar walls. Chest X-ray reveals a diffuse hazy, ground-glass appearance, usually at lung bases with poorly defined hilar densities.

*Persistent pneumonia* is defined as persistence of symptoms and roentgenographic abnormalities for more than 1 month.

*Recurrent pneumonia* is defined as two episodes of pneumonia in 1 year or more than three

episodes at any time with radiographic clearance between two episodes of illness.

Pneumonia can be classified anatomically as lobar or lobular pneumonia, bronchopneumonia and interstitial pneumonia. Pathologically there is consolidation of the alveoli or infiltration of tissue with inflammatory cells.

The cause of pneumonia depends on age, immune status and the presence of underlying chronic disease. Certain infectious agents are more common at a particular age. The causative agents of pneumonia in children according to age are given in **Table 1**.

Atypical pneumonia is caused by *Mycoplasma pneumoniae* and *Chlamydia*. Atypical pneumonia is also called as walking pneumonia.

Factors predisposing to bacterial pneumonia include increased number of siblings, parental smoking, preterm delivery, urban residence, poor socioeconomic status, impaired immune response, congenital and anatomic defects, lungs and tracheo-bronchial tree defects, cystic fibrosis, and congestive heart failure.

### ESSENTIAL DIAGNOSTIC POINTS

- Fever, cough, dyspnea
- Rales or decreased breath sounds
- Wheezing
- Myalgia, malaise
- *Abnormal chest X-ray*: Infiltrates, hilar adenopathy, and pleural effusion

## PATHOPHYSIOLOGY

Pathogens reach lungs either by hematogenous dissemination or by aspiration. Viruses are often

**TABLE 1:** Pneumonia: Pathogens in various age groups.

Age	Bacteria	Viruses	Others
Neonate	<ul style="list-style-type: none"> <li>• Group B streptococci</li> <li>• <i>E. coli</i>, <i>Klebsiella</i> spp., <i>Listeria monocytogenes</i>, <i>S. aureus</i></li> </ul>	CMV, herpes	<i>Chlamydia</i>
1–3 months	<ul style="list-style-type: none"> <li>• <i>S. pneumoniae</i></li> <li>• <i>S. aureus</i></li> <li>• <i>H. influenzae</i></li> </ul>	CMV, RSV, influenza, parainfluenza	<i>Chlamydia</i>
4 months–5 years	<ul style="list-style-type: none"> <li>• <i>S. pneumoniae</i></li> <li>• <i>S. aureus</i></li> <li>• <i>H. influenzae</i></li> <li>• Group A <i>Streptococcus</i></li> <li>• <i>Klebsiella</i></li> <li>• <i>Pseudomonas</i> sp./<i>M. tuberculosis</i></li> </ul>	<ul style="list-style-type: none"> <li>• RSV</li> <li>• Adenovirus</li> <li>• Influenza</li> </ul>	<i>Mycoplasma</i>
Over 5 years	<ul style="list-style-type: none"> <li>• <i>S. pneumoniae</i></li> <li>• <i>S. aureus</i></li> <li>• <i>H. influenzae</i></li> <li>• <i>M. tuberculosis</i></li> </ul>	<ul style="list-style-type: none"> <li>• Influenza</li> <li>• Varicella</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Mycoplasma</i></li> <li>• <i>Legionella</i> sp.</li> <li>• <i>M. catarrhalis</i></li> </ul>

responsible for bacterial infection. Following invasion of pulmonary tissue, an acute inflammatory response causes exudation of fluid and polymorphonuclear cells with eventual fibrin deposition and consolidation.

Consolidation of lung tissue decreases the vital capacity (VC) and compliance of lungs. Intrapulmonary right to left shunt and ventilation perfusion (V/Q) mismatching can cause hypoxia; even pulmonary hypertension may occur, which with added hypercapnia, can result in cardiac overload.

CLINICAL FEATURES (FIG. 1)

Cough is common symptom. It may be absent in infants and newborns. Mere observation will

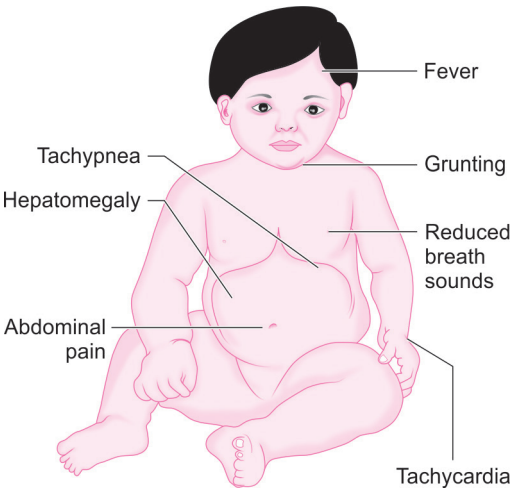


Fig. 1: Clinical features.

provide key diagnosis. Tachypnea out of proportion to the degree of fever may be the only sign in infant. Grunting respiration in young child arouse a suspicion of pneumonia.

GENERAL FEATURES

- Cough
- Vomiting
- Dehydration
- Extrapulmonary infection
- Congestive cardiac failure

Tachypnea is the most sensitive index of disease severity. The diagnosis of pneumonia is defined as respiratory rate more than 60/min in children below 2 months of age, more than 50/min in children between 2 or 12 months of age and more than 40/min in children 1–5 years of age (Table 2).

Pneumonia may present with acute abdominal pain which is attributed to referred pain from the pleura. Apical pneumonia may be associated with meningismus and convulsions.

Localized findings include inspiratory rales, reduced breath sounds and dullness to percussion. There may be associated abdominal pain, features of meningism depending on the localization of involved lung field.

*Staphylococcus* and *Klebsiella*, i.e., gram negative organism produces pneumatocele. *Pseudomonas* may produce diffuse nodular pattern in lower lobes. Anaerobic infections are also associated with lung abscess along with air/fluid levels.

Neonatal pneumonia is often difficult to recognize because of some peculiarities. These include absence of cough, fever, apneic spells, increase incidence of periodic breathing, grunting,

TABLE 2: Typical features of bacterial, viral and mycoplasmal pneumonia in children.

Items	Bacterial	Viral	Mycoplasma
Age	Any	Any	5–15 years
Season	Winter	Winter	All years
Onset	Abrupt	Variable	Insidious
Fever	High	Variable	Low grade
Tachypnea	Common	Common	Uncommon
Associated symptoms	Mild coryza Abdominal pain	Coryza	Bullous myringitis Pharyngitis
Physical findings	Evidence of consolidation	Variable	Fine crackles Wheezing
Leukocytosis	Common	Variable	Uncommon
Radiographic findings	Consolidation	Bilateral diffuse infiltrates	Variable
Pleural effusion	Common	Rare (adenovirus)	Small (10–20%)

rapid clinical deterioration, cyanosis, progressive air hunger and septicemic features.

### Pneumococcal Pneumonia

Respiratory infections due to *S. pneumoniae* are transmitted by droplets and are more common in the winter months. Bacteria multiply in the alveoli and inflammatory exudate is formed. Scattered areas of consolidation occur, which coalesce around the bronchi and later become lobular or lobar in distribution. There is no tissue necrosis.

Incubation period is 1–3 days. The onset is abrupt with headache, chills, cough, and high fever. Child may develop pleuritic chest pain. In severe cases there may be grunting, chest indrawing, difficulty in feeding and cyanosis. Bronchial breathing may be heard over areas of consolidation. Bronchophony and whispering pectoriloquy may be observed. Meningismus may be present in optical pneumonia.

X-ray findings of lobar consolidation and leukocytosis. Sputum is examined by Gram staining and culture. Blood culture may be positive in 5–10% of cases. Demonstration of polysaccharide antigen in urine is done.

### Staphylococcal Pneumonia

Staphylococcal pneumonia occurs in infancy and childhood. The pulmonary lesion may be primary infection of the parenchyma; or may be secondary to generalized staphylococcal septicemia. It may be a complication of measles or influenza; other risk factors include cystic fibrosis, malnutrition, and diabetes.

The illness is characterized by the formation of multiple pneumatoceles. The pneumatoceles fluctuate in size and finally resolve and disappear within a period of few weeks to months. Staphylococcal abscesses may erode into the pericardium causing purulent pericarditis. Empyema in a child, below 2 years of age, is nearly always secondary to staphylococcal infections.

The illness usually follows upper respiratory tract infection, pyoderma or a purulent disease.

Progression of the symptoms and signs is rapid. Pulmonary infection may occasionally be complicated by disseminated disease, with metastatic abscesses in joints, bone, muscles, pericardium, liver, mastoid or brain.

The characteristic complications of pyopneumothorax and pericarditis are highly suggestive. Pneumatoceles are present in X-ray films characteristically in pneumonia due to staphylococci or *Klebsiella*. Staphylococci can be cultured from the blood.

### Haemophilus Pneumonia

*Haemophilus influenzae* infections occur usually between the age of 3 months and 3 years and are nearly always associated with bacteremia. Infection usually begins in the nasopharynx and spreads locally or through the bloodstream. As the infants have transplacentally transferred antibodies during the first 3–4 months of life, infections are relatively less frequent during this period.

The onset of the illness is gradual with nasopharyngeal infection. Certain viral infections such as those due to influenza virus act synergistically with *H. influenzae*. The child has moderate fever, dyspnea, grunting respiration and retraction of the lower intercostal spaces.

#### THE WORLD HEALTH ORGANIZATION (WHO) GRADING OF PNEUMONIA

*Pneumonia*: Fever less than 38.5°C, no feeding difficulties, no dehydration, cough and tachypnea.

*Severe pneumonia*: High-grade fever more than 39°C, difficulty in feeding, tachypnea, respiratory distress with intercostals retraction (ICR) or subcostal retraction (SCR), dehydration, grunt, bronchial breath sounds on auscultation with or without crackles, peripheral capillary oxygen saturation (SpO<sub>2</sub>) ≥92 at room air, radiological opacity on chest X-ray.

*Very severe pneumonia*: Inability to feed, altered sensorium, intermittent apneic spells, cyanosis, excessive diaphoresis, narrow pulse pressure, academia, and SpO<sub>2</sub> < 92 at room air.

### DIAGNOSIS

Acute phase reactants, like complete blood cell (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), have poor sensitivity and specificity. They do not distinguish between viral and bacterial etiology, nor help in making decision of antibiotic choice; however, may be useful tools for monitoring the course of the disease.

Complete blood count helps for the evidence of septicemia. White blood cell (WBC) count more than 15,000 cells/cu mm, polymorphonuclear leukocytosis or count less than 5000/cu mm, or febrile neutropenia are bad prognostic signs. Nasopharyngeal aspirate is investigated for viral antigens, e.g., cytomegalovirus (CMV) and adenovirus.

Radiology is not routinely required in non-severe pneumonia to confirm the diagnosis. At times, it may correlate with the clinical signs; there is also wide variation in the interpretation by radiologists. Moreover, reliability predicting

the etiology is poor. However chest X-ray may be indicated in very severe disease, ambiguous picture, improvement/worsening more than 48–72 hours of therapy suspected complication and known immunocompromised child microbiology-sputum culture or blood culture though may be more specific, but the yield is very poor (10–15%), here is also a risk of growing normal nasopharyngeal flora.

Blood culture should be obtained before initiating the antibiotic therapy. The most reliable method for the bacterial diagnosis is culture of lung aspirate.

Circulating antigens of the streptococcal pneumonia and *H. influenzae* may be detected in blood with counter immunoelectrophoresis (CIE), polymerase chain reaction (PCR) or latex agglutination.

Diagnostic thoracentesis is done if there is significant pleural effusion. Gram staining and culture of pleural fluid is done. Bronchoalveolar lavage (BAL) should be considered in the management of severely ill child to make a prompt diagnosis.

Serology, urinary antigens, rapid antigen detection test (RADT) and cold agglutinins for mycoplasma are not easily available, expensive with time lagging and have poor sensitivity.

Invasive procedures, like bronchoscopy, BAL and lung aspiration, have high sensitivity and specificity; however, they are too invasive to be advised in office practice.

#### LABORATORY SALIENT FINDINGS

- WB count more than 15,000 cells/cu mm, polymorphonuclear leukocytosis
- *Nasopharyngeal aspirate*: Viral antigens, e.g., CMV and adenovirus
- Blood culture
- Counter immunoelectrophoresis (CIE), polymerase chain reaction (PCR) or latex agglutination
- Gram staining, culture of pleural fluid

Pulse oximetry is a mandatory tool for monitoring the course of the disease in all the hospitalized children.

Diagnosis of pneumonia is essentially clinical and seldom requires lab support. Absence of past history of recurrent cough and presence of fever with fast breathing is a hallmark presentation in clinical diagnosis of pneumonia. It should always be remembered that there are no definite differentiating markers between viral, bacterial and atypical pneumonia. However, there are certain clinical clues which can help to nail down on etiological diagnosis.

Clinical evidence of hyperinflation with scattered exudates on radiology due to segmental atelectasis.

For optimum antimicrobial management of pneumonia, it is prudent to differentiate between bacterial, viral and atypical pneumonia clinically, as it is often very difficult to isolate the offending pathogen.

Involvement of particular lobe in the chest X-ray gives the clue to etiological agent.

- Acute lobar pneumonia—pneumococcal pneumonia
- Right upper lobe pneumonia—aspiration pneumonia especially in neonate and infant
- Upper lobe pneumonia with cavitation—tuberculosis
- Multiple small abscess—staphylococcal/*Klebsiella*

## MANAGEMENT

It includes specific treatment and supportive treatment:

### Specific Treatment

It includes specific antimicrobial agent. Antibiotics are selected on the basis of age of the child, and epidemiology, clinical features, radiological features and extrapulmonary manifestation.

### Specific Antimicrobial Therapy in Pneumonia (Table 3)

- <3 months first-line; Cefotaxime/ceftriaxone ± Aminoglycosides
- 3 months–5 years first-line; Co-amoxiclav or Ampicillin + Chloramphenicol; second-line; ceftriaxone/cefotaxime
- >5 years first-line; Ampicillin/Penicillin G co-amoxiclav/Macrolide (if mycoplasma suspected); second-line; ceftriaxone/Cefotaxime and Macrolides
- Suspected staphylococcal infection; Cefuroxime or Co-amoxiclav or IV 3rd generation Cephalosporins + Cloxacillin; second-line; ceftriaxone/Cefotaxime and Vancomycin Teicoplanin/Linezolid.

**TABLE 3:** Choice of antibiotics.

Age	First-line	Second-line
3 months–5 years	Amoxicillin	Co-amoxiclav/Cefuroxime/Chloramphenicol
>5 years	Amoxicillin	Macrolode/Co-amoxiclav/Cefuroxime



If there are indications of specific etiological agents like *Chlamydia* or mycoplasma, then macrolide such as erythromycin or clarithromycin is used.

Most healthy children can be treated on outpatient setting. The most common organism responsible is *S. pneumoniae*. This will respond very well to amoxicillin (500 mg/kg/day). If there is doubt of oral intake in the beginning, injectable ceftriaxone (50 mg/kg) may be given intramuscularly at the time of diagnosis and during the first 24 hours.

Alternatively in penicillin, allergic patients' macrolide antibiotics including erythromycin (40 mg/kg in four divided doses) or azithromycin (10 mg/kg as a single dose) may be used.

Amoxicillin, ampicillin, amoxicillin-clavulanic acid, macrolides, cefuroxime axetil are the orally used antibiotics.

**Standard doses:** 40–45 mg/kg/day in two or three divided doses.

**Erythromycin:** 30–40 mg/kg/day in three divided doses.

**Clarithromycin:** 15 mg/kg/day in two divided doses.

**Azithromycin:** 10 mg/kg/day in OD dose.

For the inpatients, parenteral antibiotics should be started intravenously. Indications for admission are listed in **Box 1**. Parenteral antibiotics are continued until the patient is afebrile, has improved symptomatically and is able to take medications by mouth. The parenteral medicine can be switched over to oral medication by that time. The total duration of treatment irrespective of route of administration is 10 days.

Patients with the pulmonary complications such a pleural effusion, empyema, abscess require 2–4 weeks of antibiotic treatment. Staphylococcal empyema requires 3–4 weeks of treatment. In these high dose, parenteral therapy is given until the complication is clear. Thereafter, oral route may be used to complete the course of treatment.

#### BOX 1: Indications for admission.

- Age <1 year (lobar infiltrate)
- Respiratory compromise
- Pleural effusion (always culture by thoracentesis)
- Pneumatocele
- Failure to respond to outpatient antibiotic treatment within 24–48 hours
- Dehydration

#### Drug doses:

- *Co-amoxiclav:* 30–40 mg/kg/day
- *Ceftriaxone:* 50–100 mg/kg/day
- *Cefotaxime:* 100–200 mg/kg/day
- *Cefuroxime:* 20–30 mg/kg/day
- *Aminoglycosides:* 15 mg/kg/day in single or two divided doses

Despite rational choice of antibiotics in right dose and for optimal duration, if there is failure in clinical improvement, one needs to:

- Check the diagnosis and rule out foreign body, aspiration pneumonia and interstitial lung disease.
- Look for underlying comorbidity like lung abscess, emphysema, bronchiectasis, left to right shunts, gastroesophageal reflux disease (GERD), asthma, cystic fibrosis (CF) and ciliary dyskinesia.
- Evaluate immunosuppression in the host like human immunodeficiency virus (HIV) and hypogammaglobulinemia.

Test phagocytic dysfunctions for chronic granulomatous disease (CGD):

- Look for drug resistance, particularly if child is form of care center, has received multiple courses of beta-lactam and corticosteroids.
- Search for the possibility of polymicrobial etiology.
- There is no need to chase for follow-up X-rays since to radiological resolution may take 4–12 weeks time depending on offending organisms.

The treatment of choice for pneumococcal pneumonia is penicillin (penicillin V 250 mg q8–12h orally, penicillin G 0.5 MU/kg/day IV or procaine penicillin 0.6 MU IM daily, for 7 days), amoxycillin (30–40 mg/kg/day for 7 days) with or without clavulanic acid is a useful alternative.

Treatment of staphylococcal pneumonia includes prompt antibiotic therapy should be initiated with co-amoxiclav, or a combination of cloxacillin and a third-generation cephalosporin, e.g., ceftriaxone. If the patient does not show improvement in symptoms within 48 hours, therapy with vancomycin, teicoplanin or linezolid may be necessary. Therapy should continue till all evidence of the disease disappears both clinically and radiologically, which usually takes 2 weeks in uncomplicated cases. Therapy is continued for 4–6 weeks in patients with empyema or pneumothorax. Following initial IV therapy, the remaining course may be completed with oral antibiotics.

Treatment of *Haemophilus* infection is treated with ampicillin at a dose of 100 mg/kg/day

or coamoxiclav. Cefotaxime (100 mg/kg/day) or ceftriaxone (50–75 mg/kg/day) are recommended in seriously ill patients.

### Supportive Treatment

Paracetamol (10–15 mg/kg/dose) every 4–6 hourly for the treatment of fever is recommended. In the presence of tachypnea, cyanosis or chest indrawing, oxygen should be administered. Intravenous fluid is given if the child is not tolerating orally. Oral fluids/food is encouraged as soon as tachypnea or chest retractions are under control.

### Duration of Treatment

Pneumonia (outpatient)	- 5–7 days
Pneumonia (inpatient)	- 10–14 days
Atypical organism	- 10 days
<i>Staphylococcus pneumoniae</i>	- 3–4 weeks

### COMPLICATIONS

These include empyema, pneumothorax, bronchogenic dissemination, septicemia, osteomyelitis, multiple system abscesses, septic arthritis and meningitis.

Mortality in uncomplicated bacterial pneumonia is 1%. The most important complication is dehydration. Other complication includes in pleural effusion and empyema. Empyema may extend locally to involve pericardium, mediastinum or at the chest wall.

Electrolyte and blood urea nitrogen (BUN) can help to assess the degree of fluid loss. Extensive involvement of lung may lead to respiratory

failure. Arterial blood gases are indicated if child has severe respiratory distress or oxygen saturation less than 90%.

### PROGNOSIS

The mortality is high in younger age. Poor nutritional state like PEM Grade III and IV, extensive bilateral bronchopneumonia, associated diseases, conditions like cystic fibrosis, immunodeficiency state, malignancy, associated complication like respiratory failure and congestive cardiac failure act as poor prognostic factor.

The prognosis is usually excellent even in severe bacterial pneumonias complicated by empyema. Long-term follow-up of children with empyema has shown remarkably few, if any, residual lung function abnormalities. In contrast to adults with empyema, children seldom require surgical procedures such as decortication. Radiographic follow-up studies to document complete resolution are probably not indicated until at least 6–8 weeks have elapsed following initiation of antibiotic therapy.

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## PRESENTING COMPLAINTS

A 7-year-old boy was brought with the complaints of:

- Cough since 20 days
- Fever since 20 days
- Loss of appetite since 15 days
- Loss of weight since 10 days

## History of Presenting Complaints

A 7-year-old boy with the history of cough for 20 days was brought to the pediatric OPD. Cough was productive type. It used to be more in early morning. He used to bring out the white-colored mucopurulent copious sputum. Many a time child used to have disturbed sleep because of cough. There was also history of fever. Fever was of moderate degree, used to be more in the evening. It was not associated with chills and rigors. The boy was shown to general practitioner

and the treatment given did not relieve the fever. His appetite was decreased and mother also complained that there was loss of weight.

## Past History of the Patient

He was the second child of nonconsanguineous marriage. He was born at term by normal delivery. He was delivered vaginally. He cried immediately after the birth. The birth weight of the child was 2.75 kg. He was on breast milk exclusively for 4 months of age. Weaning started by the 4th month and was completed by 13 months. He had been vaccinated completely.

There was history of chronic cough in the father who was diagnosed to have suffering from pulmonary tuberculosis and was taking treatment.

## EXAMINATION

On examination, he was moderately built and poorly nourished. Anthropometric measurements included that his height was 120 cm (50th centile), the weight was 21 kg (50th centile).

He was febrile, pulse rate was 100 per minute and respiratory rate was 20 per minute. The blood pressure recorded was 80/70 mm Hg. There was pallor, no cyanosis and clubbing. There was no significant lymphadenopathy.

Respiratory system revealed the presence of the occasional crepitations at the base of the lungs. Other systemic examination was normal.

## INVESTIGATION

Hemoglobin	: 9.8 g/dL
TLC	: 86,000 cells/cu mm
DLC	: P <sub>56</sub> L <sub>40</sub> E <sub>8</sub> M <sub>2</sub>
ESR	: 80 mm in the 1st hour
Chest X-ray	: Suggestive of miliary mottling
Mantoux test	: Positive, i.e., induration more than 15 mm

## DISCUSSION

Cough and fever were present for 20 days. Fever was not relieved completely by a course of antibiotics.

### CASE AT A GLANCE

#### Basic Findings

Height	: 120 cm (50th centile)
Weight	: 21 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 100 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 80/70 mm Hg

#### Positive Findings

##### History

- Chronic cough
- Chronic fever
- History of contact
- Decreased appetite
- Loss of weight

##### Examination

- Febrile
- Pale
- Crepitations

##### Investigation

- Hb: 9.8 g/dL
- ESR: 80 mm in the first hour
- Chest X-ray: Miliary mottling
- Mantoux test: Positive

The child had loss of appetite and there was history of contact with the tuberculosis. Investigation report suggests the diagnosis of the primary complex. ESR is raised and Mantoux test is positive. These put collective diagnosis of tuberculosis.

Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis*. Clinical features of the disease depend on the site of the lesion, severity of infection and host resistance. The infection spread to the child, is by adult active tuberculosis patient. The usual mode of transmission is by inhalation of droplets of infected secretion. Measles, whooping cough and malnutrition will flare up the tuberculosis. But childhood tuberculosis is not contagious because of low bacterial load, and no cavitating disease.

The frequency of childhood tuberculosis depends upon:

- Number of infective cases
- Closeness of contact with infective cases
- Age of the child when exposed to tuberculosis

There are many forms of childhood TB, but common and important clinical forms are pulmonary TB, meningeal TB, military TB, and lymph node TB. Occasionally, mid-to-late adolescents are seen with cavities due to TB and they may be infectious.

## **PATHOGENESIS**

Mycobacteria are nonmotile, nonspore-forming. Pleomorphic weakly gram-positive rods are typically slender and slightly bent. The cell walls contain lipid and wax that make these organisms more resistant than most others to light, alkali, acid, and the bactericidal action of antibodies. Growth is slow, with a generation time of 14–24 hours. Acid fastness, the capacity to perform stable mycolate complexes with certain aryl methane dyes, is the hallmark of mycobacteria. Cells appear red when stained with fuchsin (Ziehl-Neelsen or Kinyoun Stain, appear purple with crystal violet, or exhibit yellow green fluorescence under ultraviolet light. Truant stain is the most sensitive method for visualizing mycobacteria in a clinical specimen.

The infection is spread by the tuberculous patient through inhalation who discharges tubercle bacilli in his sputum or nasopharyngeal secretions during bouts of coughing or sneezing, etc. Such patients are open or infective cases. In the pediatric age groups, few infections may also occur by the transplacental route (congenital tuberculosis). It can spread by direct inoculation through the skin.

After the inhalation, some bacilli remain at the site of entry. Some may be carried to the lymph nodes. The inhaled tubercle bacilli may lodge in the pulmonary alveoli. It causes hyperemia and congestion. The pulmonary alveoli are filled up with exudate comprising of fibrin leukocytes and tubercle bacilli. The central part of the inflamed area is necrosed. It looks like cheesy or caseous material. The epithelioid cell, fibroblasts and giant cells with the caseous material constitute tubercular granuloma.

The inflamed area at the point of entry of the tubercle bacilli is called as primary focus. The primary focus, the draining lymphatics and inflamed regional lymph nodes are collectively called primary complex. The areas of maximum ventilation in the lungs are usual sites of primary complex. These include right side of the lung and mid zone of the lung.

During the formation of primary complex, a few bacilli spread throughout the body by hematogenous route to form additional foci at various sites. Rich's foci is in the cortex of brain, Simon's foci in the apex of lung, Simmond's focus is in the liver, Weigart's focus is in the intima of blood vessels.

In most persons, the primary focus along with secondary foci heals, disappears, fibrosis and calcifies. Uncomplicated primary complex runs a benign course. This is because the body's immune defenses can prevent them from spreading.

Further course of the infection depends on the immune response of the host. When the cell-mediated immune response is weak, the bacilli continue to multiply and the inflammatory process extends to the contiguous areas. Progressive primary disease is a serious complication of the pulmonary primary complex (PPC) in which the PPC, instead of resolving/calcifying, enlarges steadily and develops large caseous center. The center then liquefies; this may empty into an adjacent bronchus leading to formation of a cavity. This is associated with large numbers of tubercle bacilli. From this stage, the bacilli may spread to other parts of the lobe or the entire lung. This may lead to consolidation of area of lung or bronchopneumonia.

A caseated lymph node may erode through the wall of the bronchus, leading to tuberculous bronchitis/endobronchial tuberculosis. Fibrosis and bronchiectatic changes may supervene. Discharge of the bacteria into the lumen may lead to its bronchial dissemination.

Hematogenous dissemination of *M. tuberculosis* occurs early in the course of the disease; this

results when the bacilli find their way into blood-stream through lymph nodes. This may result in foci of infection in various organs. If the host immune system is good, then these foci are contained and disease does not occur. Seeding of apex of lungs leads to development of Simon focus. Lowering of host immunity may lead to activation of these metastatic foci and development of disease. This is especially seen in young infants, severely malnourished children and children with immunodeficiency. Massive seeding of blood-stream with *M. tuberculosis* leads to miliary tuberculosis, where all lesions are of similar size. This usually occurs within 3–6 months after initial infection.

Extrapulmonary TB occurs when the quiescent disseminated foci of *M. tuberculosis* become active. The most common manifestation of extrapulmonary TB is peripheral lymphadenitis, especially of the cervical lymph nodes. Rarely, cutaneous TB can occur when an individual has had infectious substances such as sputum enter through a break in the skin.

Transmission of *M. tuberculosis* is virtually always by person-to-person spread via the respiratory route. Mucous droplets become airborne when the index case coughs, sneezes, laughs, or sings. Infected droplets dry and become droplet nuclei, which remain suspended in the air for hours. Environmental factors, such as poor air circulation, second-hand smoking, and indoor wood-burning stoves enhance transmission.

Two elements determine a child's risk for developing TB disease. The first is the likelihood of exposure to an individual with infectious TB, which is primarily determined by the individual's environment. The second is the ability of the person's immune system to control the initial infection and keep it clinically dormant. Without treatment, disease develops in 5–10% of immunologically normal adults with TB infection. In young children, the risk is greater; as many as 50% of those younger than 1 year with untreated TB infection develop radiographic or clinical evidence of TB disease. Methods of preventing disease in infected individuals benefit children and adolescents even more than adults.

About 60% of cases of childhood TB occur in infants and children younger than 5 years. The ages of 5–14 years are often called the “favored age” because children in this range may become infected, but usually have the lowest rate of TB disease. The gender ratio for TB in children is about 1:1 in contrast to adults, in whom males predominate.

Children acquire *M. tuberculosis* from adults in their environment. Environmental risk factors include those characteristics that make it more likely that the child shares the air with an adult with infectious TB. Factors that increase the risk of a child being infected with *M. tuberculosis* include: (1) birth or travel/residence in a country in which TB is endemic; (2) early childhood environments with exposures to multiple high-risk caregivers, some orphanages; or (3) contact with high-risk adults who have had previous residence in a jail, prison, or high-risk nursing home, and homelessness in some communities. Foreign visitors stay in the home, or locally defined risk factors. Factors that increase the risk of developing disease once infected include age younger than 2 years, coinfection with HIV, other immunocompromising diseases or treatments (corticosteroids, TNF- $\alpha$  inhibitors), and malnutrition.

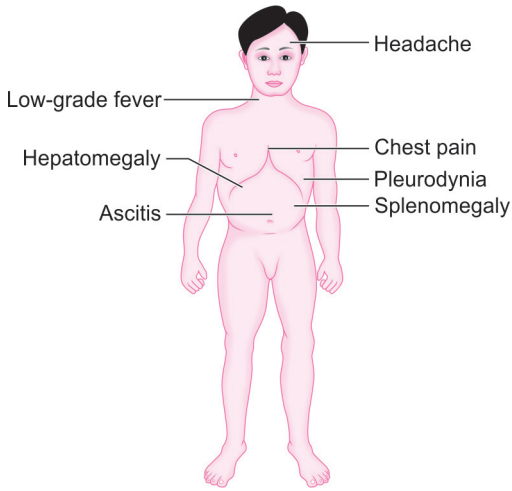
#### EVOLUTION AND TIMETABLE OF UNTREATED PRIMARY TUBERCULOSIS

Primary infection			
Febrile illness	Primary	Pleural effusion	Nodes
Erythema nodosum	Complex	Cavitation	3–9 months
Phlyctenular conjunctivitis	Primary healing	Coin shadow (73% in 6 months)	
Miliary (<5 years of age)		Renal complications after 5 years	

#### CLINICAL FEATURES (FIG. 1)

The tuberculosis infection may not cause any symptoms. Signs and symptoms with radiological findings occur once the disease occurs. The predisposing factors include measles, whooping cough, streptococcal infection, malnutrition, steroids, immunosuppressive therapy.

Primary complex leads to progressive primary complex, i.e., inflammatory process extending to contiguous areas. It occurs due to enlarged mediastinal lymph nodes. Sometimes cavity formation takes places. The inflamed lymph nodes may compress the neighboring bronchus, and produces obstruction. This leads to emphysema. Some bacilli may reach the bloodstream and dissemination occurs through the hematogenous route. The single massive seeding of the circulation with tubercle bacilli causes miliary tuberculosis.



**Fig. 1:** Clinical features.

Miliary and meningeal tuberculosis usually occur within a year of primary lesion.

Later the clinical features depend upon the site of infection.

## Pulmonary Tuberculosis

The incubation period varies between 4 and 8 weeks. The onset of symptoms is generally insidious, but may be relatively acute in miliary tuberculosis. Most symptoms in children with PPC are constitutional in the form of mild fever, anorexia, weight loss, decreased activity. Cough is an inconsistent symptom and may be absent even in advanced disease. Irritating dry cough can be a symptom of bronchial and tracheal compression due to enlarged lymph nodes. The PPC may be picked-up accidentally during evaluation of intercurrent infections.

Primary focus does not produce any clinical symptoms especially in infants and young children. In older children, it may cause vague symptoms such as malaise, fatigue, anorexia, weight loss, failure to thrive and low-grade fever. This state may be sometimes flared up by the attack, whooping cough or measles. Next step, i.e., hilar lymphadenitis may be an important feature of primary complex. The common symptoms are cough, fever and weight loss. This step can be diagnosed by positive tuberculin test (TT) and by radiological evidence.

Progressive primary complex is the result of the progression of primary disease. Children with PPC may present with high-grade fever and cough. Expectoration of sputum and hemoptysis are usually associated with advanced disease

and development of cavity or ulceration of the bronchus. Abnormal chest signs consist mainly of dullness, decreased air entry and crepitations. Cavitating pulmonary tuberculosis is uncommon in children.

Children with endobronchial tuberculosis may present with fever and troublesome cough (with or without expectoration). Dyspnea, wheezing and cyanosis may be present.

Then the progressive primary complex produces segmental lesions. The signs and symptoms depends on extent of progressive primary lesion and type of segmental lesions produced by bronchial compression or erosion. Pleural effusion occurs as a result of discharge of caseous material of peripheral (subpleural) primary focus or enlarged regional lymph node. This occurs in the patients beyond 5 years of age.

The vast majority of children with TB infection develop no signs or symptoms at any time. Occasionally, the initiation of infection is marked by several days of low-grade fever and mild cough. Rarely, the child experiences a clinically significant disease with high fever, cough, malaise, and flu-like symptoms that resolve within a week. These children have a positive test of infection, and the purpose of treating them is to prevent them from developing reactivation TB in the future.

More than 50% of infants and children with pulmonary TB have no physical findings and are discovered only via active contact tracing of an adult with TB. Infants are more likely to experience signs and symptoms because of their small airway diameters relative to the parenchymal and lymph node changes that occur. Nonproductive cough and mild dyspnea or wheezing, especially at night, are the most common symptoms. Systemic complaints such as fever, night sweats, anorexia, and decreased activity occur less often. Some infants have difficulty gaining weight or develop a true failure-to-thrive presentation that does not improve significantly until after several months of treatment.

Pulmonary signs are even less common. Some young children with bronchial obstruction have signs of air trapping, such as localized wheezing or decreased breath sounds, that may be accompanied by tachypnea or frank respiratory distress. These nonspecific symptoms and signs are sometimes alleviated by antibiotics, suggesting that bacterial superinfection distal to the focus of bronchial obstruction caused by TB has contributed to the clinical presentation of disease.

In chest radiography, the hallmark of pulmonary TB in infants and children is the relatively

large size of the hilar or paratracheal lymphadenitis as compared with the less significant size of the initial parenchymal focus. Hilar lymphadenopathy is almost invariably present with childhood TB, but it may not be distinct on a plain radiograph when calcification is not present. Significant atelectasis and/or pulmonary infiltrate make it impossible to discern the lymph node enlargement. A CT scan of the chest may show the adenopathy, but this is rarely required to establish the correct diagnosis. As the hilar or mediastinal lymph nodes continue to enlarge, partial bronchial obstruction caused by external compression from the enlarged nodes causes air-trapping hyperinflation, and even lobar emphysema. As the lymph nodes attach to and infiltrate the bronchial wall, reabsorption of air and atelectasis occurs.

The course of thoracic lymphadenopathy and bronchial obstruction can follow several paths if antituberculosis chemotherapy is not given. In many cases, the segment or lobe re-expands and the radiographic abnormalities resolve completely. However, these children are still at risk for developing reactivation TB later in life. In some cases, this segmental lesion resolves, but residual calcification of the parenchymal focus and regional lymph node occurs. Finally, bronchial obstruction may cause scarring and progressive contraction of the lobe or segment, which may be associated with cylindrical bronchiectasis and chronic pyogenic infection.

A rare but serious complication of TB in children occurs when the parenchymal focus enlarges and develops a large, caseous center. This progressive primary TB presents like bronchopneumonia and may be accompanied by high fever, severe cough, dullness to percussion, rales and decreased breath sounds. Liquefaction in the center may result in formation of a thin-walled cavity.

Adolescents with pulmonary TB may develop segmental lesions with adenopathy typical of initial infection in young children, or apical infiltrates with or without cavitation that are typical of adult reactivation TB. Regional lymphadenitis is absent in the latter type of disease. Adolescents with adult-type pulmonary TB often present with cough, fever, weight loss, fatigue, and, eventually, hemoptysis.

Tuberculous pleural effusion is uncommon in children younger than 6 years and rare in those younger than 2 years. Effusions are usually unilateral, but can be bilateral. They are virtually never associated with a segmental pulmonary lesion and are rare in miliary TB.

Tuberculous pleural effusions, which can be local or general originate from the discharge of bacilli into the pleural space from a subpleural pulmonary focus or caseated subpleural lymph node. Asymptomatic local pleural effusion is so frequent in childhood pulmonary TB that it is basically a component of the primary complex. Most large and clinically significant effusions occur months to years after the initial infection.

The clinical onset of tuberculous pleurisy is usually fairly sudden. It is characterized by low to high fever, shortness of breath and chest pain. On deep inspiration, dullness to percussion, and diminished breath sounds on the affected side. The presentation is similar to that of pyogenic pleurisy. The fever and other symptoms may last for several weeks after the start of ultimately effective antituberculosis chemotherapy. Although corticosteroids may reduce the clinical symptoms, they have little effect on the ultimate outcome. The tuberculin skin test is positive in only 70–80% of cases. The prognosis is excellent, but radiographic resolution may take months. Scoliosis rarely complicates recovery of a long-standing effusion.

### Tuberculous Lymphadenitis

It is the extension of primary lesions in the upper lung fields or abdomen. It is quite common. Constitutes about 20% of tuberculosis cervical glands are more frequently involved. This is followed axillary lymph node. Supraclavicular, tonsillar, submandibular, periauricular, axillary and inguinal lymph nodes are commonly involved. They are less severe form of extra pulmonary tuberculosis.

The gland may caseate and discharge its necrotic material into the skin. This results in exudative skin lesions. This is called as scrofuloderma. Fine-needle aspiration cytology (FNAC) or gland biopsy is done to confirm the diagnosis.

A primary focus is visible radiologically only 30–70% of the time. Tuberculin skin test results are usually reactive. Although spontaneous resolution may occur, untreated lymphadenitis frequently progresses to caseating necrosis, capsular rupture and spread to adjacent nodes and overlying skin, resulting in a draining sinus tract that may require surgical removal.

Tuberculosis of the superficial lymph nodes is the most common form of extrapulmonary TB in children. Most cases occur within 6–9 months of the initial infection, although some cases appear years later. The tonsillar, anterior cervical and submandibular nodes become involved secondary



to extension of a primary lesion of the upper lung fields or abdomen. In areas of the world, where children ingest unpasteurized products contaminated with *M. bovis*, an identical clinical entity can arise from this organism. It is important to distinguish between the two pathogens as *M. bovis* is inherently resistant to pyrazinamide, one of the first-line antituberculosis medications. Infected nodes in the inguinal, epitrochlear, or axillary regions, which are rare in children, result from regional lymphadenitis associated with TB of the skin or skeletal system.

In the early stages of infection, the lymph nodes usually enlarge gradually. The nodes are firm but not hard, discrete, and nontender. The nodes usually feel fixed to underlying or overlying tissue. Disease is most often unilateral, but bilateral involvement may occur. As infection progresses, multiple nodes are affected, resulting in a mass of matted nodes. Systemic signs and symptoms other than low-grade fever are usually absent. The chest radiograph is usually normal, although adenopathy in the chest may be apparent. Occasionally, the illness is more acute with rapid enlargement of cervical nodes, high fever, tenderness, and fluctuance. The infection may resolve if left untreated, but more often progresses to caseation and necrosis of the lymph node. The capsule of the node breaks down, resulting in the spread of infection to adjacent nodes. The skin overlying the massive nodes becomes thin, shiny, and erythematous. Rupture results in a draining sinus tract that may require surgical removal; if the correct diagnosis is made prior to rupture, however, the process can be cured with antituberculous therapy alone.

## Abdominal Tuberculosis

It is usually secondary to the primary focus in the lungs or elsewhere in the body. It may, however, be secondary to swallowing of the infected sputum by a patient with pulmonary lesions. Patients with abdominal tuberculosis may remain asymptomatic initially.

Tuberculosis of the oral cavity or pharynx is very unusual. TB of the larynx causes chronic hoarseness and is often accompanied by upper-lobe apical pulmonary disease and sputum production in adolescents and adults. TB of the esophagus is very rare in children and may be associated with a tracheoesophageal fistula.

Tuberculous peritonitis is uncommon in adolescents and rare in young children. Whereas generalized peritonitis is caused by dissemination

of organisms, most localized disease is caused by direct extension from an abdominal lymph node, intestinal focus, or tuberculous salpingitis. Initial pain and abdominal tenderness are mild. Rarely, the lymph nodes, omentum, and peritoneum become matted in children and can be palpated as a “doughy,” irregular, nontender mass. Ascites and low-grade fever are common.

Tuberculous enteritis is caused by hematogenous dissemination of organisms in most cases. However, ingestion of unpasteurized cow’s milk laden with *M. bovis* causes an identical clinical picture and is still common in many areas of the world. The jejunum and ileum near Peyer patches and the appendix are the most common sites of involvement. Mesenteric adenitis usually complicates this disease. Lymph nodes may cause intestinal obstruction or erode through the omentum to cause generalized peritonitis. This entity should be considered in any child with chronic gastrointestinal complaints and a reactive tuberculin skin test.

Symptomatic patients show evidence of tuberculous toxemia and may present with colicky abdominal pain, vomiting and constipation. The abdomen feels characteristically doughy. The abdominal wall is not rigid but appears tense, so that the abdominal viscera cannot be palpated satisfactorily. The rolled tip omentum and enlarged lymph nodes may appear as irregular nodular masses with ascites. The liver and spleen are often enlarged. Histological examination of the liver may show granulomatous hepatitis and fatty change. There are three forms of abdominal tuberculosis:

1. *Tuberculosis mesenterica*: Glandular involvement
2. *Peritonitis*: This is of two types—ascitic and plastic.  
Ascitic abdominal tuberculosis is characterized by massive ascitis. Plastic abdominal tuberculosis is characterized by chronic diarrhea, often alternating with constipation, chronic abdominal pain and growth failure.
3. *Intestinal tuberculosis*: Chronic diarrhea results as a result of epithelial ulceration.

Diagnosis is usually made on by clinical findings.

## Skeletal Tuberculosis

Skeletal TB results from lymphohematogenous seeding of tubercle bacilli during the initial infection. Bone infection also may originate as a result of direct extension from regional lymph

Node or a neighboring infected bone. The time interval between infection and clinical disease can be as short as 1 month in cases of tuberculous dactylitis, or as long as 30 months or more for TB of the hip. The infection usually begins in the metaphysis. Granulation tissue and caseation destroy bone by direct infection and by pressure necrosis. Soft tissue abscess and extension of the infection through the epiphysis into the nearby joint often complicate the bony lesion.

Weight-bearing bones and joints are most commonly affected. The majority of cases of bone TB occur in the lower thoracic and upper lumbar vertebrae, causing TB of the spine or Pott disease. Involvement of two or more vertebrae is common; these vertebrae are usually contiguous, but there may be skip areas between lesions. Infection in the body of the vertebra leads to bony destruction and collapse. The infection may extend out from the bone, causing a paraspinal, psoas, or retropharyngeal abscess. The most frequent clinical signs and symptoms of tuberculous spondylitis in children are low-grade fever, irritability, and restlessness, especially at night; back pain; and abnormal positioning in gait or refusal to walk. Spinal rigidity may be caused by profound muscle spasm.

Other sites of skeletal TB, in approximate order of frequency, are the knee, hip, elbow, and ankle. The degree of involvement can range from mild joint effusion without bone destruction to frank destruction of bone and restriction of the joint caused by chronic fibrosis. The tuberculin skin test is reactive in 80–90% of cases, and culture of joint fluid or bone biopsy usually yields the organism.

Tuberculous dactylitis is a form of bone TB that is peculiar to infants and toddlers. Affected children develop distal endarteritis followed by painless swelling and cystic bone lesions in the hands.

It occurs in children if the primary tuberculosis is inadequately treated or untreated. The commonly involved bones are thoracic vertebrae. Other sites are hips, knee, small bones of hand, feet. Kyphosis and gibbus formation leads to paraplegia. Tuberculosis of bones and joints are almost always due to late hematogenesis spread from the primary complex in the lung. The common sites are spine, hip and knee joint.

## Renal Tuberculosis

It is another late manifestation of hematogenous spread. It takes around 4–5 years after the primary infection. The symptoms include frequency of

micturation, dysuria, sterile pyuria and painless hematuria. Hydronephrosis will be caused by involvement of renal pelvis and ureter.

## Skin Tuberculosis

It may be in the form of erythema nodosum. Tuberculous ulcers are characterized by undermined edge. Tuberculomas are tiny papules with concave surface. They may be multiple. Scrofuloderma is the involvement of skin overlying the caseous lymph node.

## Miliary Tuberculosis

It usually occurs within first few months. It is common below the age of 4 years. The disease is more severe in younger age. Tuberculous meningitis occurs in about 20% of miliary tuberculosis. Miliary tuberculosis occurs as a result of hematogenous dissemination. It is characterized by extensive miliary mottling of lungs and involvement of spleen, liver and other tissues.

The lymphohematogenous spread of bacilli that accompanies the initial infection is usually asymptomatic. Patients rarely experience protracted hematogenous TB caused by the intermittent release of tubercle bacilli as a caseous focus erodes through the wall of the blood vessel in the lung. Although the clinical picture may be acute, more often, it is indolent and prolonged, with high fevers accompanying the release of organisms into the bloodstream. Early pulmonary involvement is surprisingly mild, but diffuse lung involvement becomes apparent if treatment is not given promptly.

The most common clinically significant form of disseminated TB is miliary disease, which occurs when massive numbers of bacilli are released into the bloodstream, causing disease in at least two organs. This form of disease usually occurs within 2–6 months of the primary infection. The clinical manifestations are protean, depending on the number of organisms that disseminate and the focus of infection. Lesions are usually larger and more numerous in the lungs, spleen, liver, and bone marrow than in other organs. This form of TB is most common in infants and in malnourished or immunosuppressed patients.

The onset of clinical disease is sometimes explosive, with the patient becoming gravely ill in several days. More often, the onset is insidious, with the patient not being able to pinpoint the true time of initial symptoms. The most common signs include malaise, anorexia, weight loss, and



low-grade fever. Within several weeks, hepatosplenomegaly and generalized lymphadenopathy develop in about 50% of cases. About this time, the fever may become higher and more sustained, but the chest radiograph is usually normal and respiratory symptoms are few. Within several more days to weeks, the lungs become filled with tubercles, causing dyspnea, cough, rales, and wheezing. As pulmonary disease progresses, alveolar air block syndrome may result in frank respiratory distress, hypoxia, and pneumothorax or pneumomediastinum. Signs or symptoms of meningitis or peritonitis are found in 20–40% of patients with advanced disease. Severe headache in a patient with miliary TB usually indicates the presence of meningitis. Abdominal pain or tenderness is usually a sign of tuberculous peritonitis. Choroid tubercles occur in patients and are highly specific for miliary TB. Unfortunately, the tuberculin skin test is nonreactive in as many as 50% of patients with advanced disease. Chest X-ray is characteristic of demonstrating multiple minute dots. This has been described as “snowstorm” appearance. BCG test is often positive.

## CNS Tuberculosis

Central nervous system (CNS) disease is the most serious complication of tuberculosis in children and arises from the formation of a caseous lesion in the cerebral cortex or meninges that results from occult lymphohematogenous spread. Infants and young children are likely to experience a rapid progression to hydrocephalus, seizures and raised intracranial pressure. In older children, signs and symptoms progress over the course of several weeks, beginning with fever, headache, irritability and drowsiness. The disease advances with symptoms of lethargy, vomiting, nuchal rigidity, seizures, hypertonia and focal signs. The final stage of disease is marked by coma, hypertension, decerebrate and decorticate posturing and death.

Central nervous system TB is the most serious complication in children and is fatal without effective treatment. This condition can arise from massive hematologic dissemination of organisms, but usually arises from the formation of a caseous lesion in the cerebral cortex or meninges that develops during the occult lymphohematogenous dissemination of the initial infection. This lesion, called a Rich focus, increases in size and discharges small numbers of tubercle bacilli into the subarachnoid space. The resulting exudate may infiltrate the cortical or meningeal

blood vessels, producing inflammation, obstruction, and subsequent infarction of the cerebral cortex. This exudate also interferes with the normal flow of cerebrospinal fluid (CSF) in and out of the ventricular system at the level of the basal cisterns, leading to a communicating hydrocephalus. The combination of vasculitis, infarction, cerebral edema, and hydrocephalus results in severe damage that occurs gradually or rapidly. Abnormalities in electrolyte metabolism, especially hyponatremia caused by syndrome of inappropriate antidiuretic hormone or salt wasting, also contribute to the pathophysiology.

Tuberculous meningitis complicates about 0.3% of untreated TB infections in children. This condition is extremely rare in infants younger than 3 months because pathologic events usually need this much time to develop. It is most common in children between 6 months and 4 years of age.

The clinical progression of tuberculous meningitis may be rapid or gradual. Rapid progression occurs more frequently in infants and young children who may experience symptoms for only several days before the onset of acute hydrocephalus, seizures, and cerebral edema. More often, the signs and symptoms progress slowly over several weeks, and can be divided into three stages. The first stage, which typically lasts 1–2 weeks, is characterized by nonspecific symptoms such as fever, headache, irritability, drowsiness, and malaise. Focal neurologic signs are absent, but infants may experience a stagnation or loss of developmental milestones. The second stage usually begins more abruptly. Lethargy, nuchal rigidity, Kernig’s and Brudzinski’s signs, seizures, hypertonia, vomiting, cranial nerve palsies relevant to basilar meningitis, and other focal neurologic signs are apparent. This clinical picture usually correlates with the development of hydrocephalus, increased intracranial pressure, and vasculitis. The third stage is marked by coma, hemiplegia or paraplegia, hypertension, decerebrate posturing, deterioration in vital signs, and, eventually, death. The prognosis of tuberculous meningitis correlates closely with the clinical stage of illness at the time treatment with anti-tuberculosis chemotherapy and corticosteroids begins.

The majority of patients in the first stage have an excellent outcome, whereas most patients diagnosed in the third stage who survive have permanent disabilities, including blindness, deafness, paraplegia, and mental retardation. It is imperative that antituberculosis chemotherapy

be considered for any child who develops basilar meningitis and hydrocephalus or cerebral infarction with no other apparent etiology. The key to diagnosis is often identifying the adult from whom the child acquired *M. tuberculosis*.

Another manifestation of central nervous system TB is the tuberculoma, which presents clinically as a brain tumor. Tuberculomas account for as many as 40% of brain tumors in children in some areas of the world. These lesions, which occur most often in children younger than 10 years, are usually singular, but they may be multiple. In adults, lesions are usually supratentorial, but in children, they are often infratentorial, located at the base of the brain near the cerebellum. The most common symptoms are headache, fever, and seizures. The paradoxical development of tuberculomas in patients with tuberculous meningitis while receiving effective chemotherapy has been recognized since the advent of CT. The cause and nature of these tuberculomas are poorly understood, but their development does not require a change in the therapeutic regimen. Whenever a child with tuberculous meningitis deteriorates or develops focal neurologic findings while on treatment, this phenomenon should be considered. Corticosteroids may help alleviate the occasionally severe clinical signs and symptoms. These lesions may be very slow to resolve clinically, persisting radiographically for months or years.

#### ESSENTIAL DIAGNOSTIC POINTS

- A chronic infectious disease caused by *Mycobacterium tuberculosis*
- The infection spread to the child is by adult active tuberculosis patient
- Measles, whooping cough and malnutrition will flare up the tuberculosis
- The primary focus, the draining lymphatics and inflamed regional lymph nodes are collectively called primary complex
- Primary complex lead to progressive primary complex, i.e., inflammatory process extending to contiguous areas
- Congenital tuberculosis is suspected if the mother is known to have tuberculosis recently diagnosed
- Erythrocyte sedimentation rate is raised
- Mantoux test is positive
- Chest X-ray suggests primary complex

### Cardiac Tuberculosis

Tuberculous pericarditis occurs in infected children. It arises from hematogenous dissemination or direct invasion from caseous lymph nodes in the subcarinal area. Pericardial fluid may be serofibrinous or hemorrhagic. Extensive fibrosis

of the pericardial sac may lead to obliteration with development, usually years later, of constrictive pericarditis. The presenting systems are usually nonspecific: low-grade fever, poor appetite, failure to gain weight, and chest pain. A pericardial friction rub may be heard, or, if large effusion already is present, distant heart sounds, tachycardia, and narrow pulse pressure may suggest the diagnosis.

### Congenital Tuberculosis

Congenital tuberculosis is suspected if the mother is known to have tuberculosis recently diagnosed, if the broad-spectrum antibiotics are ineffective and congenital infections are negative.

Symptoms may be present at birth. They are also seen in the 2nd and 3rd week. Hepatosplenomegaly respiratory distress, fever, lymphadenopathy are present.

The fetus can be infected in utero via the umbilical cord. Placental infection results from dissemination in the mother. This results in hematogenous congenital tuberculosis. There are certain criteria that include tuberculosis lesions in the infant and one of the following:

- Lesions in the 1st week of life
- Primary hepatic complex or caseating granuloma
- Documented tuberculosis infection of the placenta or endometrium
- Exclusion of tuberculosis by a carrier in the postnatal period.

*M. tuberculosis* can pass from the placenta to the fetus through the umbilical vein. The mothers of these infected infants frequently suffer from tuberculous pleural effusion, meningitis, or disseminated disease during pregnancy or soon afterward. However, the diagnosis of TB in the newborn often leads to the discovery of the mother's TB. Initial infection in the mother just before or during pregnancy is more likely to lead to congenital infection than previous infection. However, even massive involvement of the placenta with TB does not usually give rise to congenital infection. The tubercle bacilli first reach the fetal liver, where an initial focus develops with associated involvement of regional lymph nodes. Organisms then pass through the liver into the main fetal circulation, leading to foci in the lung and other tissues. The bacilli in the lung usually remain dormant until after birth, when oxygenation and pulmonary circulation increase significantly. Congenital TB also may occur by aspiration or ingestion of infected amniotic fluid if a caseous placental lesion ruptures directly into the amniotic cavity.

Symptoms of true congenital TB may be present at birth, but more commonly begin in the 2nd or 3rd week of life. The most common signs and symptoms, in order of frequency, are respiratory distress, fever, hepatic or splenic enlargement, poor feeding, lethargy or irritability, lymphadenopathy, abdominal distention, failure to thrive, ear drainage, and skin lesions. Many infants have an abnormal chest radiograph, most often a miliary pattern. Only one-third of affected infants have meningitis. This clinical presentation in newborns is similar to that caused by bacterial sepsis and other congenital infections. The diagnosis of neonatal TB should be suspected in an infant with signs and symptoms of bacterial or congenital infection whose response to antibiotic and supportive therapy is poor and whose mother has risk factors for developing TB.

Diagnosis depends on clinical suspicion and demonstration of acid-fast bacilli in tissue or fluids. Early morning gastric washings, open lung biopsy are used to establish the diagnosis. Chest X-ray shows military pattern.

Aspiration of infected amniotic fluid during or at the time of delivery leads to direct congenital tuberculosis.

#### GENERAL FEATURES

- Asymptomatic
- Poor built
- Fatigue
- Loss of appetite
- Chronic cough
- Convulsion

### TUBERCULOSIS AND HIV INFECTION

In general, the clinical presentation of TB in children with HIV infection is similar to that in children without HIV infection. However, children with HIV infection more commonly have extrapulmonary TB (especially meningitis, tuberculoma, and abdominal disease), and pulmonary TB has a more aggressive picture, more often leading to substantial infiltrates or cavitation within the lung. Establishing the diagnosis of TB in an HIV-infected child can be difficult because the skin test is often negative, microbiologic confirmation of disease is difficult to achieve in many cases, and other opportunistic conditions can mimic TB. An aggressive evaluation for TB should be undertaken for any child with known HIV infection, or risk factors for HIV infection, who develops pulmonary disease or any unusual constellation of signs and symptoms.

### DIFFERENTIAL DIAGNOSIS

- Typhoid
- Malaria
- Malignancy
- Urinary tract infection
- Collagen disorders
- Cirrhosis
- Rheumatic fever

### DIAGNOSIS

High index of suspicion is of considerable importance. Tuberculosis should be suspected in the presence of growth failure, malnutrition, pyrexia of unknown origin (PUO), prolonged cough, recurrent chest infections, painless lymphadenopathy, asthma, pleural effusion, pneumonia not responsive to antibiotics for pyogenic infections and unsatisfactory recovery from illnesses such as typhoid, whooping cough or measles.

Both IGRAs contain negative and positive controls in addition to the *M. tuberculosis*-specific antigens. These are used in test interpretation. A positive result is defined as when the difference in the amount of IFN- $\gamma$  measured between the test antigen and the negative control is greater than a certain threshold: over 8 spots in T-SPOT. TB and greater than 0.35 IU/mL in QFT. Too, much IFN- $\gamma$  response to the negative control or too little response to the positive control yields indeterminate (QFT) or invalid (T-SPOT.TB) results. For the QFT failure to shake, the sample as per manufacturer instruction increases the likelihood of an indeterminate result. Other factors associated with indeterminate results include young age and immunocompromised status.

In many clinical situations, these tests have a higher specificity than the TST, better correlation with surrogate measures of recent exposure to *M. tuberculosis* in low-incidence settings, and less cross-reactivity than the TST with previous BCG vaccination. Two clear advantages of the IGRAs are the need for only one patient encounter (two with the TST) and the lack of possible boosting of the result because the patient is not exposed to any biologic material. However, the sensitivity of IGRAs is similar to the TST, which ranges from 50 to 84% in studies of culture-proven TB disease in children.

Diagnosis of TB in children poses a problem due to the varied clinical presentation of TB and since infection is paucibacillary isolation of TB bacilli is difficult.

Diagnosis is primarily passed on indirect clues such as clinical history and examination,

family or contact history, radiographic abnormalities, immunization status, fine-needle aspiration cytology/biopsy.

## Bacteriological Diagnosis

### Smear Examination

Demonstration of *M. tuberculosis* or its components. The organism can be demonstrated by: (i) Ziehl-Neelson (ZN) staining; (ii) special stains; (iii) cultures; (iv) polymerase chain reaction (PCR); and (v) other methods.

The above methods can be used on sputum, induced sputum, gastric lavage, bronchoscopic lavage fluid, or pleural fluid. The best specimen for demonstration of *M. tuberculosis* in children is the early morning gastric aspirate obtained by using a nasogastric tube before the child arises. The yield on ZN stain is less than 20% and depends on extent of pulmonary disease. For better results, at least two consecutive specimen of gastric aspiration are recommended.

Diagnosis is by clinical features, presence of contact in the family history, positive TT, and suggestive findings on chest X-ray. Demonstration of *M. tuberculosis* in a specimen from lungs is the gold standard but it is not always present.

*Specimens for demonstration of M. tuberculosis:* In pulmonary tuberculosis, specimens to be collected are sputum, gastric lavage, bronchoscopy lavage fluid or pleural fluid. Recent reports suggest good results of isolation of *M. tuberculosis* from induced sputum. The latter can be safely and effectively performed in infants and young children. Induced sputum provides a satisfactory and more convenient specimen for bacteriological confirmation of pulmonary tuberculosis in both HIV-infected and uninfected children.

*Method of sputum induction:* Child is pretreated with 200 µg of salbutamol given via metered dose inhaler with attached spacer or nebulizer to prevent the occurrence of bronchoconstriction. A jet nebulizer attached to oxygen at a flow rate of 5 L/min or compressor can be used to deliver 5 mL of 3% sterile saline for 15 minutes. Sputum is obtained either by expectoration in children (who are able to cooperate) or by suctioning through the nasopharynx or oropharynx using in sterile, mucus extractor or catheter size six. Specimen should be transported directly to the laboratory for processing.

*Gastric lavage:* Early morning gastric aspirate (GA) obtained by using a nasogastric tube before the child wakes up and peristalsis empties the stomach of the respiratory secretions swallowed

overnight is the best specimen for demonstration of *M. tuberculosis*. For higher yield, specimen should be neutralized with sodium bicarbonate, if a delay in processing specimen is expected.

*Bronchoscopy and bronchoalveolar lavage:* This has got no advantage over properly done GA. Bronchoscopy may be considered when there is doubt in diagnosis or a possibility of resistant tuberculosis is considered.

Young children are not able to provide sputum. In them, sputum can be induced. Following an overnight fast, the patient receives salbutamol by nebulizer followed by hypertonic saline (3% or 5%) inhalation by nebulizer. Older children may provide expectoration at end of procedure. In young children including infants, a nasopharyngeal aspirate is collected and processed like sputum for smear and culture to identify *M. tuberculosis*.

### Smear staining:

1. *ZN staining:* Yield is 20% and depends on the extent of pulmonary disease and number of specimens tested.
2. *Special staining for acid-fast bacillus (AFB):* Fluorochrome-stained smears can be viewed more efficiently.
3. *Auramine O staining.*

Detection of acid-fast bacilli by ZN staining or fluorescent microscopy of sputum, gastric contents, laryngeal swabs, needle aspiration from areas of lung consolidation, lymph node, pleural, ascitic fluid, and CSF is the best way to diagnose TB.

### Culture Examination

Cultures should only be obtained if source patient is likely to have drug resistance, if bacteriological conversion or deterioration occurs during a course of supervised short course chemotherapy, in extrapulmonary TB and in immunocompromised children. Material can be sent for culture in Lowenstein-Jenson (LJ) medium. Microscopic examination of thin layer culture plate may lead to detection of microcolonies of *M. tuberculosis* as early as after 7 days.

Excessively long period required for isolation of *M. tuberculosis* by conventional culture techniques has led to the development of other techniques for culture such as BACTEC radiometric assay, Septicheck AFB system and mycobacterial growth indicator tube (MGIT) system. In this system, culture is positive in majority by the end of 2 weeks though the final result is available by the end of 6 weeks.



### Rapid Direct Tests

Polymerase chain reaction, PCR is the most commonly used technique of nucleic acid amplification, for diagnosis of tuberculosis. The PCR may be used to: (i) diagnose tuberculosis rapidly by identifying DNA from *M. tuberculosis* in clinical samples that are negative by microscopic examination; (ii) determine rapidly whether acid-fast organisms identified by microscopic examination in clinical specimens are *M. tuberculosis* or atypical *Mycobacteria*; and (iii) identify the presence of genetic modifications known to be associated with resistance of some anti-mycobacterial agents. PCR is a suitable technique in childhood tuberculosis, especially when diagnosis is difficult or needed urgently.

### Serology and Antigen Testing

Enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA) testing for detection of antibodies immunoglobulin G (IgG), immunoglobulin M (IgM) to mycobacterial antigens. The sensitivity and specificity depends on the type of antigen used, prevalence of tuberculosis and recent BCG vaccination. Antigens like A60 which have less crossreactivity have been found to have good sensitivity and specificity particularly in TB meningitis. They may be useful in diagnosis of extrapulmonary TB.

### Radiological Diagnosis

The typical chest X-ray appearance of a pulmonary primary complex is that of an airspace consolidation of variable size, usually unifocal and homogeneous. Enlarged lymph nodes are usually seen in the hila, right paratracheal region. Adenopathy alone may be the sole manifestation of primary tuberculosis. There is no consensus regarding the most common site of involvement. Consolidation in PPC is usually heterogeneous, poorly marginated predilection of involvement of apical or posterior segments of upper lobe or superior segment of lower lobe.

In infected children, the chest radiographs may be normal or may demonstrate lobar, segmental involvement, multifocal involvement, hilar lymphadenopathy, pleural effusion, obstructive air trapping, military shadows, cavities, pericardial effusion. Both lateral and posteroanterior views should be done since enlarged hilar nodes may be missed otherwise. In miliary TB, the chest radiograph changes may lag behind the clinical findings, so an initial negative film may bear

repeating in the appropriate clinical case (cryptic military TB).

Occasionally, the chest radiograph may be normal and lymphadenopathy may be detected on computed tomography (CT). In addition, CT features such as low attenuation lymph nodes with peripheral enhancement, lymph node calcification, branching centrilobular nodules and miliary nodules are helpful in suggesting the diagnosis in cases where the radiograph is normal or equivocal. Other features such as segmental or lobar consolidation and atelectasis are nonspecific. Contrast-enhanced MRI is emerging as a very useful technique for diagnosing CNS tuberculosis, as it demonstrates the localized lesions, meningeal enhancement and the brainstem lesions.

X-ray skull may reveal silver beaten (also termed as copper beaten) indicates raised intracranial tension and/or calcification when the tuberculosis is present.

### Tuberculin Test

Robert Koch first proposed tuberculin, a broth culture filtrate of tubercle bacilli in 1880. In 1908, Mantoux described this intradermal test. Mantoux test can deliver tuberculin into the skin, the Heaf test or the Tine test. Reactivity to tuberculin is found if a person has been exposed to mycobacteria and has intact cell-mediated immunity.

Tuberculin test is merely an index of infection, the degree of its positivity and local ulceration are no indication of an active-disease or extent of disease. The degree of hypersensitivity is generally high in recently infected individual the reaction of TT must be considered in relation to:

- Duration of onset of hypersensitivity, and
- Prevalence of nonspecific tuberculous sensitivity.

*Mantoux test:* 1TU (PPD RT23 with Tween 80) is used. It is injected intradermally on an area of healthy skin, away from obvious blood vessels on the left forearm; Site should not be swabbed with spirit or antiseptic but washed and dried at the junction of upper and middle third skin.

A tuberculin syringe with needle 25 gauge is used intradermally, with bevel upward to produce 5–8 mm diameter wheal, which disappears within 1 hour. If no wheal is produced, the injection is too deep. It is read at 48–72 hours (any reaction observed before 48 hours may not be tuberculin hypersensitivity and should be ignored). It is read by locating area of induration, measuring diameter not erythema with calliper or transparent ruler.

Mantoux test is considered positive if:

*Reaction 5 mm is positive:* Patients with HIV, patients with fibrotic lesions on chest radiograph, close contacts of infectious tuberculosis.

*Reaction 10 mm is positive:* Recent converters >10 mm increase over 2 years in, intravenous drug users known to be HIV negative, patients with predisposing medical conditions such as diabetes, immunosuppressive drugs, patients from high prevalence countries.

*Reaction >15 mm is positive:* For all others.

*Interpretation:* Positive reaction reading, i.e., exceeding 10 mm, indicates the following:

- BCG already given to the child
- Infection under 2 years of age, under 6 years of age provided the child is exposed to a known case of tuberculosis, recent conversion from negative to positive.

Children with Mantoux reading of over 20 mm have high chances of a demonstrable pulmonary lesion.

*False-negative reaction:* Due to depressed sensitivity, an individual may show false negative tuberculin reaction, despite the presence of tuberculosis, in the following situations:

- Poor technique
- Incubation period
- Advanced tuberculosis, e.g., miliary tuberculosis, tuberculous meningitis, etc.
- Convalescence from whooping cough or measles
- Steroid therapy
- Leukemia
- Leprosy
- Severe malnutrition

*False-positive mantoux test:*

- Ruptured small venule
- Secondary infection
- Faulty interpretation (i.e., measurement of erythema)
- Recent blood transfusion

### BCG Diagnostic Test

There has been increasing documentation about the value of BCG vaccination as a diagnostic tool. It is believed to be far superior to TT. Its basis is hypersensitivity.

The appearance of a papule, more than 5 mm in diameter, during the first 24–72 hours, indicates a positive test. The grading is as follows:

- *5–10 mm diameter:* Mildly positive
- *10–20 mm diameter:* Moderately positive
- *Above 20 mm diameter:* Strongly positive

The advantages of BCG as a diagnostic measure are:

- It is a very sensitive and reliable test.
- It is generally positive even in situations such as miliary tuberculosis, tuberculous meningitis and severe malnutrition where Mantoux test is often false-negative despite the presence of tuberculosis.

### Fine-needle Aspiration Cytology

This simple diagnostic technique is now increasingly being employed and gives gratifying information.

Biopsy may show a granuloma formation with giant cells and epithelioid cells and central caseation which is more characteristic of tuberculosis.

### Diagnostic Algorithm

The diagnosis of tuberculosis disease in children continues to be challenging. Even in advanced nations, the diagnosis is most often made by combination of a positive tuberculin skin test, chest radiograph, physical examination and history of contact with adult patient with tuberculosis. Newer diagnostic methods such as PCR and serodiagnosis have not given encouraging results. Newer staining and culture methods have found their place in the management of tuberculosis. There is a need to develop better techniques for diagnosis of tuberculosis in children.

### Kenneth Jones Diagnostic Criteria

In 1960, Kenneth Jones devised a scoring system for diagnosis of childhood tuberculosis. The system is helpful in arriving at exact diagnosis.

#### LABORATORY SALIENT FINDINGS

- Detection of acid-fast bacilli by Ziehl–Neelsen staining
- Enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA) testing for detection of antibodies IgG, IgM to mycobacterial antigens
- Polymerase chain reaction
- Fine-needle aspiration cytology
- Radiological diagnosis
- Tuberculin test
- Mantoux test
- BCG test
- CT scan

The diagnosis of the tuberculosis is based on clinical features, history of contact with open infective cases, demonstration of hypersensitivity to tuberculin, evidence of the radiological lesions

**TABLE 1:** Kenneth Jones diagnostic criteria for childhood tuberculosis.

Score (+3)	Score (+2)	Score (+1)	Score (–1)
<ul style="list-style-type: none"> <li>• Demonstrable bacilli</li> <li>• Tuberculous granuloma</li> <li>• Positive Mantoux test</li> </ul>	<ul style="list-style-type: none"> <li>• Suggestive chest X-ray</li> <li>• Suggestive physical findings</li> <li>• Doubtful Mantoux test (5–9 mm)</li> <li>• Recent Mantoux conversion from negative to positive</li> <li>• Contact with sputum positive patient</li> </ul>	<ul style="list-style-type: none"> <li>• Nonspecific changes in chest X-ray</li> <li>• Compatible physical findings</li> <li>• History of contact</li> <li>• Nonspecific granuloma</li> <li>• Age under 2 years</li> </ul>	BCG vaccination during the preceding 2 years

and laboratory investigation, i.e., TT. It is useful for diagnosis. Most frequently used tests are Mantoux test and multiple puncture test—Heaf test (**Table 1**).

## TREATMENT

An ideal antituberculous drug need to possess three characters namely: (1) potent bactericidal activity against metabolically active bacilli, (2) sterilizing activity against semidormant persisting bacilli, and (3) potential to prevent emergence of resistant organisms throughout the period of chemotherapy.

Antitubercular drugs are the mainstay of treatment. *First-line drugs:* Isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin.

*Second-line drugs:* Cycloserine, ethionamide, PAS, capreomycin and kanamycin.

*Other drugs:* Quinolones, rifamycin, amikacin, imipenem and ampicillin.

Mycobacteria replicate slowly and remain dormant in the body for prolonged periods. The treatment of TB is affected by the, presence of naturally occurring drug-resistant organisms in large bacterial populations, even before chemotherapy is initiated. This drug resistance is caused by mutation at one of several chromosomal loci. The loci for resistance to one drug are not linked to the loci for resistance to other antituberculosis drugs.

These microbiologic characteristics of *M. tuberculosis* explain why single antimicrobial drugs cannot cure TB disease in adults. The major biologic determinant of the success of antituberculosis therapy is the size of the bacterial population within the host. For patients with a large population of bacilli, such as adults with cavities or extensive infiltrates, many drug-resistant organisms are present initially, and at least two antituberculosis drugs must be given. Conversely, for patients with infection but no disease, the bacterial population is small, drug-resistant organisms are rare or nonexistent, and

a single drug, such as isoniazid, can be given. Children with pulmonary TB and patients with extrapulmonary TB have medium-size populations in which significant numbers of drug-resistant organisms may or may not be present. In general, these patients are treated with at least two, and usually three or four, drugs.

## Drugs for Tuberculosis

### Isoniazid

Isoniazid (INH), a synthetically produced drug, is the most potent and valuable single drug in the treatment of TB. An oral dose attains a plasma concentration 20–80 times the usual level required to inhibit the growth of tubercle bacilli (0.02–0.05 µg/mL) within several hours, with, high concentrations persisting for 6–8 hours in plasma and sputum. Isoniazid penetrates readily into the CSE, even in the absence of inflammation, and into caseous tissue. It is partially conjugated in the liver to an acetylated, inactive, non-toxic form. The rate and degree of acetylation are genetically determined.

The principal side effects of isoniazid are peripheral neuritis and hepatitis. Peripheral neuritis results from competitive inhibition of pyridoxine metabolism. This is more likely to occur at higher dosages of isoniazid 10 mg/kg/day) in alcoholics and people who are poorly nourished. This is rarely a problem in children, although precautions must be taken during adolescence, for breastfeeding babies, during pregnancy, or when the total daily dose of isoniazid exceeds 300 mg. Pyridoxine (10 mg for each 100 mg of isoniazid) should be given daily when indicated.

Other infrequent adverse effects of isoniazid are convulsions (usually from a large and often intentional overdose), psychoses, loss of memory, allergic manifestations, and a lupus-like syndrome with arthritis and antinuclear antibodies.

### Rifampicin

Rifampicin is a semisynthetic drug that has wide antimicrobial activity against bacteria



and mycobacteria. It is absorbed readily from the gastrointestinal tract after oral administration, with peak concentrations of 6–32 µg/mL (mean inhibitory concentration for *M. tuberculosis*, 0.5 µg/mL) occurring in 3 hours. Rifampicin readily diffuses to, most tissues and body fluids; CSF levels are low but adequate for treatment. It is excreted primarily through the biliary tract and kidneys.

Rifampicin is relatively nontoxic; the principal side effect is hepatitis, which occurs with a frequency of <1%. Hepatitis seems to be more common in patients who are treated with the combination of rifampicin and isoniazid: Gastrointestinal disturbances, rashes, reversible leukopenia, thrombocytopenia, and elevation of blood urea nitrogen have been reported.

Administration of the drug may also impart an orange-red color to feces, urine, sputum, saliva, tears, and sweat. The suggested dosage is 10–20 mg/kg/day (maximum 600 mg). A liquid preparation is not commercially available, but can be prepared in community pharmacies. A newer, longer-acting rapamycin called rifapentine is now available for use in combination with longer-acting for treatment of TB infection. It is not used in treatment of TB disease in children. It has the same drug interactions and adverse effects as rifampicin.

### *Pyrazinamide*

Pyrazinamide (PZA) is a bactericidal drug that attains a therapeutic concentration in the CSF and in macrophages. It is recommended as the third drug of a three or four-drug regimen, particularly for the first 2 months of therapy. In doses of 20–40 mg/kg/day (adult dose, 2 g/day), it is well tolerated by children. Adverse reactions are rare in children but may include hepatitis, joint pain (caused by elevated levels of uric acid), and itching with or without a rash.

### *Ethambutol*

Ethambutol is an odorless water-soluble compound rapidly absorbed from the gastrointestinal tract and excreted in the urine, mainly with its form unchanged. It is bacteriostatic at the usual dose of 20 mg/kg/day. It is excreted via the kidneys and must be used with caution in patients with renal dysfunction. The only important toxic effect is a retrobulbar neuritis that infrequently results in loss of visual acuity, defects in visual fields, and inability to distinguish between red and green; the visual changes are usually reversible. This side

effect should be monitored by monthly studies of visual acuity and visual fields and tests for green color vision when possible. At doses of 20 mg/kg/day, it can be safely administered to children of all ages. Ethambutol is used as the fourth drug in a multidrug regimen, and its major purpose is to prevent emergence of resistance to other drugs.

### *Corticosteroids*

These drugs are controversial in the management of TB. They can be used only if effective antituberculosis therapy is in place. They are useful when the host inflammatory response to *M. tuberculosis* contributes to tissue damage. Generally accepted indications are for the management of tuberculous meningitis, tuberculous pleural effusion, pericarditis and endobronchial disease. Prednisone at 2 mg/kg/day is used commonly for 4–6 weeks and then weaned slowly.

### *Second-line Drugs for Resistant M. tuberculosis*

The emergence of multidrug-resistant *M. tuberculosis* strains means that second-line drugs must be used to treat children who have acquired these strains. Second-line drugs also can be used if children are intolerant of the first-line drugs. An expert in TB should be consulted, whenever a second-line drug is being considered for a child.

Second-line drugs are divided into several classes: the injectables, the fluoroquinolones, oral bacteriostatic agents, and other agents. These classes are used to determine the treatment regimens for drug-resistant TB, generally using one from each class to comprise three to four drugs active against the individual's isolate. First-line drugs with activity against the isolate are also used.

The fluoroquinolones, specifically levofloxacin and moxifloxacin, have bactericidal activity against *M. tuberculosis*. They also penetrate the tissues and central nervous system well. Side effects include neuropsychiatric issues, joint problems, Achilles-Tendon inflammation and rupture (rare in children), and prolonged QT interval. Levofloxacin is available as an oral suspension for younger children, whereas moxifloxacin must be compounded into a suspension. If an isolate is resistant to one fluoroquinolone, then it is likely resistant to the other.

Streptomycin, capreomycin, amikacin, and kanamycin comprise the injectable class of second-line drugs. The injectable drugs are nephrotoxic,

can cause hearing loss after prolonged use, and are quite painful when administered as intramuscular injections. The WHO recommends that children with milder forms of multidrug-resistant disease can forego the injectable drugs as their risks may outweigh the benefit.

**The oral:** Bacteriostatic agent class includes cycloserine and the closely related terizidone, prothionamide and the closely related ethionamide, as well as para-aminosalicylic acid (PAS). The fifth class includes other agents: clofazimine (used often in the treatment of *Mycobacterium leprae*, the etiologic agent responsible for leprosy, or Hansen disease), meropenem, and linezolid. Two newly developed drugs, bedaquiline and delamanid, are being studied for their use in adult MDR-TB but can be used on a compassionate-release basis for children.

### Indications for Specific Chemotherapy

- All children with demonstrable active tuberculous lesions, e.g., progressive primary complex, pleural effusion, miliary tuberculosis, meningitis, etc.
- All children below 5 years of age having positive tuberculin/BCG had not been already given to them
- All children whose tuberculin/BCG test has recently converted positive, provided BCG had not been given to them a few months back
- All unprotected children (BCG not given) who are exposed to open cases of tuberculosis.

### Short Course Chemotherapy

Short course chemotherapy is given in two phases:

1. *Initial intensive phase:* Here three or four drugs are employed on daily basis.
2. *Follow-up phase:* Here two or three drugs are given, twice or thrice a week to reduce toxicity and improve compliance by the patient.

### Indian Academy of Pediatrics on ATT Regimens

The Indian Academy of Pediatrics (IAP) recommendations on antitubercular treatment (ATT) are given in the **Table 2**.

#### Prednisolone

**Role of steroids in TB:** Corticosteroids, in addition to antitubercular drugs, are useful in treatment of patients with CNS tuberculosis and occasionally pulmonary tuberculosis. These are useful in settings where the host inflammatory reaction contributes significantly to tissue damage. Short-courses of corticosteroids are indicated in children with endobronchial tuberculosis that causes localized emphysema, segmental pulmonary lesions or respiratory distress. Some children with severe miliary tuberculosis may show dramatic improvement with corticosteroids, if alveolocapillary block is present. While significant improvement in symptoms can occur in children with pericardial effusion, steroids do not alter outcome of pleural effusion. The most commonly used medication is prednisolone, at doses of 1–2 mg/kg/day for 4–6 weeks.

Drug	Daily dose (mg/kg)	Route of administration	Side effects
Isoniazid	5 (preferably as a single dose)	Oral	Constipation, weight gain, euphoria, peripheral neuritis, convulsions, pellagra-like skin lesions, hepatotoxicity, very rarely bone marrow depression and toxic encephalopathy
Streptomycin	20–50	Intramuscular	Deafness (eight cranial nerve involvement), nephrotoxicity. It may cause severe and, at times, fatal reaction in HIV-positive subjects
Thiacetazone	2–3	Oral	Hepatotoxicity, skin lesions, agranulocytosis
Rifampicin	10–20	Oral	Rarely hepatotoxicity intermittent administration may be accompanied by thrombocytopenia and leucopenia, an influenza-like illness and respiratory syndrome
Ethambutol	15–20	Oral	Anaphylactoid reactions, peripheral neuritis, hyperuricemia, retrobulbar neuritis
Pyrazinamide	30	Oral	Hepatotoxicity, gout
Ethionamide	15–20	Oral	Nausea, vomiting, pain abdomen
Ciprofloxacin	10	Oral	Hypersensitivity, arthralgia
Amikacin	7.5	Intravenous, intramuscular	Nephrotoxicity

**TABLE 2:** Indian Academy of Pediatrics (IAP) recommendations on treatment of childhood tuberculosis.

<b>Group 1 (Preventive Therapy)—6HR</b>
<ul style="list-style-type: none"> <li>Asymptomatic Mantoux positive &lt;3 years</li> <li>Asymptomatic Mantoux positive &lt;5 years with grades III or IV malnutrition</li> <li>Mantoux –ve</li> <li>Recent converter/no signs (Healed lesion—normal chest X-ray or calcification/fibrosis)</li> <li>Children &lt;3 years with history of +ve contact</li> <li>Children &lt;5 years grades III or IV malnutrition with history of +ve contact</li> </ul>
<b>Group 2—2 HRZ/4 HR</b>
<ul style="list-style-type: none"> <li>Primary complex (Lungs)</li> <li>Symptomatic Mantoux +ve &lt;3 years—without localization</li> <li>Symptomatic Mantoux +ve &lt;5 years with grades III or IV malnutrition—without localization</li> <li>Isolated lymphadenitis</li> <li>Pleural effusion</li> </ul>
<b>Group 3—2 HRZE/4 HR</b>
<ul style="list-style-type: none"> <li>Progressive pulmonary disease</li> <li>Tubercular lymphadenitis—multiple (In case of nonresolution of lesion, extend continuation phase by 3 months)</li> </ul>
<b>Group 4—2 HRZE/7 HR</b>
<ul style="list-style-type: none"> <li>Miliary/disseminated disease</li> <li>Cavitary disease/bronchopneumonia</li> <li>Osteoarticular disease</li> <li>Abdominal, pericardial, genitourinary disease</li> </ul>
<b>Group 5—2 HRZE/10 HRE</b>
Neurotuberculosis

Prednisolone 1–2 mg/kg (double the usual dose to take care of Rifampicin steroid interaction of for 4–6 weeks is used in TB meningitis (Stage 2 and 3), pericardial TB, seriously ill miliary TB, and mediastinal lymph nodes causing airway compression. Steroids may also necessary for severe hypersensitivity reactions to several antitubercular drugs. Topical steroids are used in eye, skin and joint TB.

#### Indications

- Neurotuberculosis
- Miliary tuberculosis
- Tuberculosis involving serous layers
- Endobronchial tuberculosis/segmental lesions
- Genitourinary tuberculosis/sinus formation

**Dose:** 1–2 mg/kg/day for 4–8 weeks (neurotuberculosis 8–12 weeks)

#### BCG adenitis

- If lymph node is small (<1.5 cm), no treatment is required.
- Increasing size or fluctuant:* Excision or 3–6 hours
- Sinus formation:* Excision

### MANAGEMENT OF AN INFANT BORN TO MOTHER WITH TUBERCULOSIS

It is difficult to differentiate between congenital and postnatally acquired tuberculosis. Infants born to mothers with active tuberculosis should be screened for evidence of disease by physical examination, TT and X-ray film of chest. If physical examination and investigations are negative for disease, the infant should receive isoniazid prophylaxis at doses of 10 mg/kg/day for 6 months.

After 3 months, the patients should be examined for evidence of infection and a repeat TT is done. If TT is negative, the infant can be immunized with BCG and INH can be stopped. If TT is positive but the infant is asymptomatic, INH prophylaxis is continued for another 3 months. Infants with congenital tuberculosis should be treated with four drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) in the intensive phase followed by two drugs (isoniazid and rifampicin) during maintenance phase for next 4 months.

### MANAGEMENT OF A CHILD IN CONTACT WITH AN ADULT WITH TUBERCULOSIS

Nearly one-third of children (aged less than 5 years) in contact with adults with active tuberculosis disease may have evidence of tuberculosis infection. The infection is more commonly associated with younger age, severe malnutrition, absence of BCG vaccination, contact with an adult who is sputum positive and exposure to environmental tobacco smoke. Children below 5 years of age in contact with adult patients with pulmonary tuberculosis should be treated with INH prophylaxis at a dose of 10 mg/kg/day for 6 months.

### MONITORING THE TREATMENT

Response to treatment can be judged using the following criteria: Clinical, radiological, bacteriological, and laboratory test.

#### Clinical Criteria

Clinical improvement assesses the response of therapy. The child should be seen every

2–4 weeks initially, then every 4–8 weeks. On each visit, improvement in fever, cough, appetite and subjective well-being is assessed. The child is examined for weight gain and improvement in chest findings. Compliance is assessed by talking to parents and checking medications on each visit. Majority of children show improvement in symptoms within a few weeks.

In the presence of poor response or worsening of symptoms or signs, the initial basis of diagnosis is reviewed, especially, if there are no problems with compliance. Assessment for possibility of drug resistant tuberculosis should be made. After the treatment is over, follow up every 3–6 months for next 2 years is desirable.

### Radiological Criteria

Clinical improvement precedes radiological clearance of lesion on chest X-ray films. The first chest X-ray during therapy should be done after 8 weeks, i.e., at the end of intensive phase. In patients who show increase or little change in radiological features coupled with delayed clinical response, prolongation of intensive phase by 1 month is suggested. Further films are taken after 4 weeks and child, if better, should be shifted to continuation phase; else the child is investigated for failure of treatment and drug resistance. The degree of radiological clearance can be graded as: (i) complete clearance, (ii) moderate-to-significant clearance (1/2–2/3 clearance), and (iii) mild clearance (decrease in size); or (iv) no clearance or appearance of new lesion.

### Microbiological Criteria

Most childhood pulmonary tuberculosis is paucibacillary. In children, where isolation of *M. tuberculosis* was possible at the time of diagnosis, every effort should be made to document disappearance of bacilli during therapy.

## TREATMENT OF EXPOSURE AND INFECTION

Children exposed to potentially infectious adults with pulmonary TB should be started on treatment with isoniazid if the child is younger than 5 years or has other risk factors for the rapid development of TB disease. Failure to do so may result in the development of severe TB even before a test of infection becomes positive; the “incubation” of disease may be shorter than that for the test. The child is treated for a minimum of 3 months after contact with the infectious case is broken.

After 3 months, the test of infection is repeated. If the second test is positive, infection is documented and isoniazid should be continued for a total of 9 months; if the second test is negative, the treatment can be stopped.

Two circumstances of exposure deserve special attention. A difficult situation arises when exposed children are generic because of HIV infection or other immune-compromise. These children are particularly vulnerable to rapid progression of TB, and it may not be possible to tell whether infection has occurred. In general, these children should be treated as if they have TB infection. The second situation is potential exposure of a newborn to a mother or other adult with possible pulmonary TB.

In general, this exposure should be treated the same as for an older infant. The neonate should be started on isoniazid and continued on it until TB disease in the adult can be ruled out, or for 3 months after the person with TB is no longer contagious.

Historically, treatment consisted of 9 months of isoniazid, but in recent years, new regimens have become available. Isoniazid is usually taken every day, but can be administered twice weekly under the direct observation of a healthcare worker in cases of high-risk infection, particularly if an adult with TB disease who is also being treated twice a week is present in the home.

The summary opinion of experts is that 9 months of therapy is the optimal length of treatment for children with TB infection. The major difficulty with taking isoniazid for 9 months is completing the regimen. Rifampicin taken daily for 4 months is effective, and completion rates with this regimen are much higher compared to those with 9 months of isoniazid. The rifampicin regimen causes fewer adverse events, but as children typically tolerate isoniazid well, there is little difference between the two regimens in terms of safety.

The newest treatment for TB infection is a 12-dose, once-a-week regimen consisting of isoniazid and the long-acting rifamycin rifapentine; this regimen is referred to as 3 HP. This has been studied in children 2–17 years of age; it is well tolerated and at least as effective as 9 months of isoniazid taken daily. Adults occasionally develop a flu-like illness, joint pains, and/or skin rash caused by the rifapentine, but these are extremely rare in children. Currently, 3 HP may be limited in availability and, in many locales, is available only via directly observed therapy given by the local health department.

If a child is exposed to or infected with an isoniazid-resistant but rifampicin-susceptible strain of *M. tuberculosis*, rifampicin should be given for 4 months. If the infecting strain is resistant to both isoniazid and rifampicin, a fluoroquinolone-based treatment regimen is often used, but an expert in TB should be consulted for this situation.

## DRUG-RESISTANT TUBERCULOSIS

The treatment of MDR-TB requires minimum of 3 new drugs. Kanamycin (15 mg/kg), Cycloserine (10 mg/kg), Ethionamide (15 mg/kg), para aminosalicylic acid (150–200 mg/kg) can be used. There is limited data on use of quinolones in TB in children but they may be used as an additional drug along with the above second-line drugs.

- Sputum examination for AFB should be done after 2 months of second-line drugs and monthly if positive till the 6th month as delayed conversion of sputum is also known. Once sputum smear and culture becomes negative repeat sputum examination is advised every 3–6 months till completion of the regimen. Once it becomes negative, the injectable drugs should be omitted and at least two oral drugs to be continued for at least 12 months and maximum for 18–24 months.
- Radiology does not play a significant role in the guide to the management of MDR-TB. Cough and hemoptysis are also not significant. However, fever plays a very important role in assessing the response or failure of the drug regimen.

## NEWER ANTITUBERCULOUS DRUGS

In view of increasing resistance to commonly used antituberculous drugs, it is vital to discover newer agents that have antituberculous activity against resistant bacilli. Currently, some agents have emerged as promising antituberculous drugs for use in selected cases.

### NEWER ANTITUBERCULOUS DRUGS

- **Quinolones** Ciprofloxacin, ofloxacin, norfloxacin, pefloxacin, sparfloxacin, lomefloxacin, enoxacin
- **Rifampicin derivatives** Rifabutin, rifapentine
- **Beta-lactams with beta-lactamase inhibitors:** Amoxicillin with clavulanic acid, ticarcillin with clavulanic acid, ampicillin with sulbactam
- **Aminoglycosides:** Kanamycin, amikacin, capreomycin
- **Macrolides:** Clarithromycin

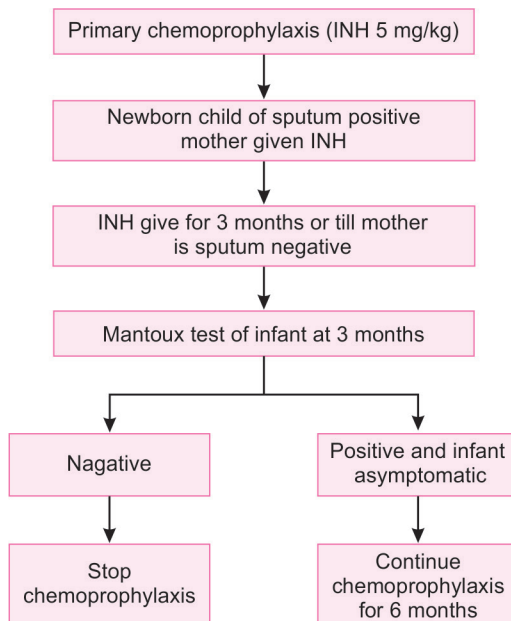
**Steroids:** In selected cases (tuberculous meningitis, severe intrathoracic tuberculosis-like pleural effusion and extensive endobronchial disease), steroids may be given in a dose of 1–2 mg/kg/day for 2–4 weeks.

**Prevention:** Chemoprophylaxis in TB.

Chemoprophylaxis is administration of drugs to prevent occurrence of active disease. Usually, isoniazid in the dose of 5 mg/kg/day is given for a duration of 6 months. This gives protection from active disease in 90% of cases.

Chemoprophylaxis is of two types:

1. **Primary chemoprophylaxis:** It is intended to prevent TB infection. It is indicated in the newborn child of a sputum positive mother. Usually, it is given till the mother becomes sputum negative (3 months). Once the mother is sputum negative and the infant is asymptomatic but Mantoux test is positive, chemoprophylaxis is continued for a total duration of 6 months.
2. **Secondary chemoprophylaxis:** It is infact treatment of subclinical infection. It is indicated in Mantoux positive patients, asymptomatic high-risk group patient without evidence of active disease such as recent converters to Mantoux positive, old healed fibrotic lesions on chest radiology, HIV positive patients, chronic renal failure, hematological malignancies, and patients on corticosteroids or cytotoxic drugs.





Preventive therapy using two or more agents (i.e., INH and RMP, or PZA and fluoroquinolone such as Ciprofloxacin) for 12 months can be considered in cases involving exposure to drug-resistant source cases.

The only available vaccine against TB is BCG, which employs live attenuated bacilli. The BCG vaccines are extremely safe in immunocompetent hosts. BCG vaccination given during infancy has little effect on the ultimate incidence of TB among adults in a population. However, many experts believe that BCG vaccines are more effective in preventing disseminated TB among infants and young children. Retrospective studies from Europe and Asia yielded estimates of the protective effect of BCG in young children of 60–80%, and the effect is particularly strong for tuberculous meningitis and severe forms of disease.

The BCG vaccines are among the safest of the childhood vaccines. Many children develop a small local ulceration, but regional suppurative lymphadenitis occurs in only 0.1–19% of vaccines. These lesions usually resolve spontaneously, but occasionally require chemotherapy with either isoniazid or erythromycin. Rarely, needle aspiration or surgical incision and drainage of the suppurative draining node is necessary, but this should be avoided rather than encouraged. Systemic complaints such as fever, convulsions, and irritability are extraordinarily rare after BCG vaccination. Children with undiagnosed serious immunocompromising conditions (e.g., severe combined immunodeficiency) can develop systemic and even fatal infection after neonatal BCG vaccination.

## SURGERY

Indications of surgical intervention, greatly minimized over the years, are summarized below:

### INDICATIONS FOR SURGERY IN TUBERCULOSIS

- Biopsy
- Abscess formation
- Bronchiectasis (secondary)
- Cavity formation with persistently positive sputum
- Chronic fibrosis
- Constrictive pericarditis
- Structural defects especially ureteric strictures
- Perforation of an ulcer
- Gastrointestinal hemorrhage
- Obstructive lesion
- Shunt procedure for obstructive hydrocephalus
- Pott spine with compression symptoms and signs
- Cold abscess
- Ascites
- Pleural effusion

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# Atrial Septal Defect

## PRESENTING COMPLAINTS

A 7-year-old boy was brought with the complaints of:

- Cold since 7 days
- Cough since 7 days
- Fever since 3 days
- Tiredness since 3 days

## History of Presenting Complaints

A 7-year-old boy was brought to the pediatric outpatient department with the history of repeated respiratory tract infection. He used to have respiratory illness involving cough, cold, and fever almost once in every month. Sometime it occurs still more often. He was admitted on 3–4 occasions. Many a time, he required parenteral antibiotics. Mother also told that her son would be much tired after some unaccustomed work, i.e., there was effort intolerance.

### CASE AT A GLANCE

#### Basic Findings

Height	: 120 cm (50th centile)
Weight	: 21 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 106 per minute
Respiratory rate	: 32 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Repeated respiratory tract infection
- Effort intolerance

##### Examination

- Pallor
- Parasternal heave
- Fixed split of second sound
- Ejection systolic murmur
- Crepitations at the base of lungs

##### Investigation

- Hemoglobin: 8 g/dL
- ECG: Right ventricular hypertrophy
- X-ray chest: Mild-to-moderate cardiomegaly

## Past History of the Patient

He was the second sibling of nonconsanguineous marriage. He was born at full term after normal delivery. He cried immediately after the delivery. There was no significant postnatal event. The mother and child were sent home on 3rd day. He was taking breast milk. Weaning was started as per the advice of the family doctor. All the developmental milestones were normal. His academic performance in school was good, but he never used to take part in sports.

## EXAMINATION

Child was moderately built and nourished. He was attentive and was answering very promptly. Anthropometric measurements included, the height was 120 cm (50th centile), then weight was 21 kg (50th centile).

The child had temperature, i.e., 38°C pulse rate was 106 per minute, the respiratory rate was 32 per minute. The blood pressure recorded was 70/50 mm Hg. There was pallor, but there was no icterus, no cyanosis and no edema. There was no significant lymphadenopathy.

Cardiovascular system revealed the presence of the parasternal heave. There was systolic thrill. The first heart sound was normal. There was split in second heart sound. Ejection systolic murmur was present at the left second and third intercostal space.

Respiratory system revealed the presence of crepitations at both the bases. Per abdomen examination was normal.

## INVESTIGATION

Hemoglobin	: 8 g/dL
TLC	: 8,500 cells/cu mm
DLC	: $P_{72} L_{26} M_4$
ESR	: 22 mm in the 1st hour
ECG	: Showed volume overload of the right ventricle, right axis deviation, and right ventricular hypertrophy

X-ray chest : Showed mild-to-moderate cardiomegaly and pulmonary vascularity

## DISCUSSION

It is an abnormal communication between two atria. There are three types: one is ostium secundum—generally located at the fossa ovalis, and second is ostium primum—located inferior to the fossa ovalis. Sinus venosus occurs in about 10% of all atrial septal defects (ASDs). Most commonly is located at the entry of superior vena cava into right atrium and is associated abnormal venous return as location of venosus is intimately related right upper pulmonary vein. Ostium secundum is more commonly seen, occurs in 10% of patients with congenital heart disease.

The defect is more often sporadic but may be familial or have genetic basis (Holt-Orm syndrome). After third decade, atrial arrhythmias or pulmonary vascular disease may develop. Irreversible pulmonary hypertension resulting cyanosis as atrial level shunting becomes right to left ultimately right heart failure can occur (Eisenmenger syndrome).

In ASD secundum, a defect is seen in midatrial septum.

In ASD primum, it is a defect in lower atrial septum.

Sinus venosus defect is seen in posterosuperior atrial septum.

Interference with the development of the atrial septum at its lower margin, associated with abnormal development of the endocardial cushions produces an ostium primum atrial septal defect. This lesion is generally associated with abnormalities of the mitral and tricuspid valves (which form from the endocardial cushions) as well as defective formation of the upper portion of the interventricular septum.

A second type of atrial septal defect is the ostium secundum defect. This is a defect in the central portion of the septum in relation to the foramen ovale; it results from inadequate closure of the central hole in the septum primum by the septum secundum and is more appropriately termed a fossa ovalis defect.

A third type of atrial septal defect is the sinus venosus defect—that is, in the superior portion of the atrial septum—and generally extends into the superior vena cava. With sinus venosus defects there may be right-to-left shunting from the superior vena cava into the left atrium because of

deficiency in the upper part of the septum where it normally meets the superior vena cava, and slight arterial oxygen desaturation may be found.

## Incompetent (Patent) Foramen Ovale

With the onset of ventilation after birth, pulmonary venous return increases markedly, and left atrial pressure rises. The foramen ovale is therefore normally functionally closed by the membranous valve of the foramen ovale, opposed to; the crista dividens and the lower portion of, the septum secundum. Although typically functionally closed shortly after birth, the foramen ovale remains probe-patent or larger in 30% of people. When pulmonary vascular resistance does not fall normally after birth, the resultant pulmonary hypertension and increased right ventricular end-diastolic pressure and right atrial pressure often cause right-to-left shunting across the foramen ovale and systemic hypoxemia.

In some infants, although the normal atrial pressure relationships occur after birth, the valve of the foramen ovale does not completely cover the foramen, either because the valve is too short or because the foramen ovale has become enlarged and stretched in infants in whom left atrial pressure and volume are increased, as with patent ductus arteriosus, ventricular septal defect, or left ventricular outflow obstruction secondary to aortic stenosis or coarctation. Significant left-to-right shunting may occur through an incompetent foramen ovale when left atrial pressure is high. If the cause of the increased left atrial pressure is relieved, atrial shunting generally decreases or disappears.

In some congenital heart defects, survival after birth depends on persistent patency of the foramen ovale. These defects include tricuspid, aortic, and mitral atresia and total anomalous pulmonary venous connection. In aortopulmonary transposition, a patent foramen ovale may be the only communication between the systemic and pulmonary circulations. Right-to-left shunting across the foramen ovale is also associated with right ventricular obstructive lesions, such as pulmonic stenosis, and with pulmonary hypertension, particularly in newborns.

## Ostium Primum Defect

Ostium primum defect (partial AV canal defect) is the most benign form of endocardial cushion defect. The central portion of the atrial septum in the region of the mitral and tricuspid valve rings

is absent, and the defect is usually large. The anterior (or septal) mitral valve leaflet is displaced and usually cleft. The tricuspid valve is generally not involved but may also have a small cleft in the septal leaflet. The magnitude of the left-to-right shunt is controlled by the same mechanisms in ostium primum as in secundum atrial septal defects.

### Ostium Secundum Defect

Ostium secundum defects vary in size from a small defect to one in which only a rim of atrial tissue separates the defect from the AV valves. Usually, ostium secundum defects are isolated lesions, but some may be associated with partial anomalous pulmonary venous connection (usually draining the right lung) or pulmonic stenosis.

Small atrial communications are associated with small shunts. Such small defects are common at birth. Defects under 3 mm in diameter almost all close spontaneously, as do a high percentage of those from 5 to 6 mm diameter. Some defects become larger. Large defects are associated with large left-to-right shunts if there is low inflow resistance of the right ventricle and a low pulmonary resistance. The effect of a large shunt at the atrial level is a marked increase in flow through the right atrium and right ventricle. This extra volume load is tolerated well by the right ventricle because it is handling the increased volume at a low pressure. Therefore, cardiac failure is unusual in infancy and, when it occurs, is generally precipitated by either a combination of defects, associated cardiomyopathy, or some other complication such as severe anemia. Persistent right-to-left shunting is unusual in ostium secundum defects, but transient right-to-left shunting is common after any Valsalva-like maneuver.

This results in the leaking of blood from left atrium to right atrium. There is not much difference in the pressure between two atria. Thus left-to-right shunt is silent. The right atrium receives the blood from left atrium also. It enlarges to accommodate the extra flow. The large volume received by the right atrium passes through the normal tricuspid valve. This produces delayed diastolic murmur. This is heard best at lower left sternal border. The right ventricle enlarges in size to accommodate the volume of blood. Because large volume of the blood passes across the normal pulmonary valve produces the pulmonary ejection murmur.

#### ESSENTIAL DIAGNOSTIC POINTS

- Right ventricular heave
- S<sub>2</sub> widely split and fixed
- Grade I–III/IV ejection systolic murmur at pulmonary area
- Diastolic flow murmur at the lower left sterna border
- ECG with rsR lead VI

### CLINICAL FEATURES (FIG. 1)

These children are generally silent, and asymptomatic. Mild effort intolerance and frequent respiratory tract infections are common. Congestive cardiac failure is rare.

Peripheral pulses are normal and equal. Heart is hyperactive with parasternal impulse is present. Systolic thrill may be palpable along with the second left interspace. The first sound is normal and may be accentuated. Second sound is widely split. The pulmonary valves close late and P<sub>2</sub> is delayed. There will be further increase in right ventricular volume during inspiration and hence there will be further delay in P<sub>2</sub>. Therefore second sound is widely split and fixed. The pulmonary artery and its branches enlarge to accommodate the left-to-right shunt. Hence, lung fields appear plethoric. The split is fixed due to right ventricular stroke volume being equal in both inspiration and expiration.

The size of the left-to-right shunt is directly proportional to the intensity of two murmur and heart size. Larger shunt will have more cardiomegaly and louder the pulmonary and tricuspid murmur.

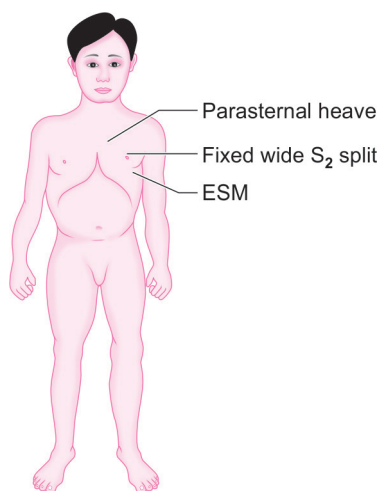


Fig. 1: Clinical features.

The clinical features with ostium primum are similar and include right ventricular hyperactivity, increased pulmonary flow, and a widely split second sound. In addition to the right ventricular outflow murmur and the tricuspid mid-diastolic flow murmur, murmurs of mitral or tricuspid regurgitation, or both, may be present.

Children with ostium secundum, large atrial septal defects are generally asymptomatic. However, when there is pulmonary hypertension because of congenital or acquired lung disease, especially in preterm infants, the atrial septal defect may contribute to the symptoms as well as to right-to-left intracardiac shunting. The increased right ventricular volume load causes precordial hyperactivity along the left sternal border. The first heart sound is normal, and the second heart sound is characteristically widely split, with absence of the normal respiratory variation in the width of splitting. Both components of the second sound are of normal intensity. Although fixed splitting of the second sound is characteristic in older children, this sign is occasionally absent, especially in infants or when the communication is not large.

Ejection systolic murmur is heard at second and third left intercostal space. There is mid-diastolic murmur in the fourth intercostal spaces lower left sternal border. This is caused by increased flow across the tricuspid valve during diastole.

Flow across the atrial septal defect is not associated with a murmur. However, a long systolic ejection murmur that is crescendo-decrescendo (ejection) in type is generally heard at the upper left sternal border as a result of increased flow across the right ventricular outflow tract and pulmonic valve. The murmur associated with atrial septal defects can usually be differentiated from an innocent pulmonary flow murmur, which is usually shorter, by the response to the Valsalva maneuver. When intrathoracic pressure is increased, systemic venous return is immediately reduced, right ventricular stroke volume decreases immediately, and the intensity of an innocent pulmonary flow murmur suddenly decreases.

However, with a large atrial septal defect; the left-to-right shunt across the atrial communication maintains right ventricular stroke volume for several beats despite the decrease of systemic venous return; thus, there is little, if any, change in the intensity of the murmur in the first 3 to 4 beats. If the left-to-right shunt is fairly large, there is often a low-frequency, rumbling, early or mid-diastolic murmur caused by increased flow across

the tricuspid valve and heard best at the lower left sternal border. A prominent third heart sound is often heard at the lowest left sternal border.

Spontaneous closure occurs in ASD less than 3 mm before one and a half years of age. If the defect is more than 8 mm, spontaneous closure is doubtful. Infective endocarditis does not occur in isolated ASDs.

Therefore prophylaxis against infective endocarditis is not required.

## DIAGNOSIS

The electrocardiogram in ostium primum characteristically shows left axis deviation, generally in the 20° to 60° range, and right ventricular hypertrophy with an rsR pattern in right precordial leads. Chest radiographic findings depend on the magnitude of left-to-right shunting. Two-dimensional echocardiography and color Doppler flow mapping usually clearly delineate the anatomy. Congestive heart failure and arrhythmias occur, usually in late teenage or early adult life.

The chest radiograph in ostium secundum shows enlargement of the right atrium and ventricle and sometimes the outflow region of the right ventricle. The main pulmonary artery is dilated, and pulmonary vascular markings are increased. However, the relationship between prominence of the pulmonary vascularity and the magnitude of the left-to-right shunt is unreliable. The electrocardiogram generally shows right axis deviation with normal atrial complexes and normal conduction. There is right ventricular hypertrophy with a typical rsR or rSR pattern in the right precordial leads, and the S wave in the inferior leads is usually notched.

Two-dimensional echocardiography in ostium secundum shows an increase in diastolic size of the right ventricle together with paradoxical motion of the interventricular septum. Other similar hemodynamic disturbances, such as partial anomalous pulmonary venous return and pulmonary or tricuspid regurgitation, may give similar findings. Septal dropout is often seen, indicating the site of the atrial septal defect, and color Doppler clearly demonstrates the flow patterns and often the defect. A negative shadow in the right atrium during contrast echocardiography can delineate the defect.

Flow velocity is increased depending upon the shunt which brings dilatation of pulmonary artery and enlargement of right atrium and right ventricle. M-mode ECHO may show increased right ventricular dimension and paradoxical

motion of interventricular septum. It signifies right ventricular volume overload—characteristic flow pattern with maximum left-to-right shunt occur in diastole. Color flow mapping evaluates hemodynamic state of ASD. Doppler examination estimates presence in right ventricular and pulmonary artery.

#### GENERAL FEATURES

- Asymptomatic
- Effort intolerance
- Repeated respiratory infection

#### LABORATORY SALIENT FINDINGS

- The ECG is characterized by right axis deviation and right ventricular hypertrophy.
- Right ventricular hypertrophy (RVH) and right bundle branch block (RBBB) with rSR pattern in V1 is typical.
- Radiograph of chest shows mild-to-moderate cardiomegaly, right atrial and right ventricular enlargement, prominent main pulmonary artery segment
- Echocardiogram especially M-mode shows increased size of the right ventricle with paradoxical ventricular septal motion.

## COMPLICATIONS

Secundum ASD is well tolerated. Atrial arrhythmias, heart failure, pulmonary arterial hypertension are the main complications.

## TREATMENT

Medical management includes treating the chest infections. Definitive cure is by operation. The ideal age for operation is 2–5 years to prevent heart failure and arrhythmias in later life. The risk of operation is 1%. Infective endocarditis is very rare.

Surgical closure of the primum defect and repair of the cleft mitral valve has low risk and high effectiveness, but postoperative subaortic stenosis is common. Some patients develop severe hemolysis from red cell trauma if a small deficiency in the mitral valve leaflet directs a high-pressure

jet at the atral patch. At times, hemolysis improves, but some patients require reoperation to abolish the hemolysis.

Surgical or catheterization closure is generally recommended for symptomatic children, with large atrial level defect and associated with right heart dilatation.

Surgical indication include left-to-right shunt. Some consider small shunt to be an indication because of danger of paradoxical embolization and cerebrovascular accident. Another indication for surgery is left-to-right shunt with QP/QS of more than 1.5.

High pulmonary vascular resistance (PVR) more than 10 units/m<sup>2</sup> is a contraindication to surgery.

Surgery is usually delayed till 3–4 years, because of spontaneous closure. But if CCF in infancy does not respond to medical management, then surgery is indicated. The defect is repaired under cardiopulmonary bypass with either simple suture or a pericardial or a Teflon patch.

Postoperative complications include arrhythmias and cerebrovascular accidents. The risk of operation is 1%. There is greater risk of small infants and those with high PVR.

Postoperative follow-up include atrial and nodal arrhythmias. These occur in 7–20%. Sick sinus syndrome may supervene especially when sinus venosus defect is repaired. This eventually may require antoarrhythmic drug or pacemaker implantation.

## COURSE AND PROGNOSIS

Pulmonary hypertension and reversal of shunt are rare late complications. Spontaneous closure occurs, most frequently in children with defect less than 4 mm in diameter.

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# Coarctation of Aorta

## PRESENTING COMPLAINTS

A 4-year-old boy was brought with the complaints of:

- Swelling of the face since 6 months
- Headache since 6 months
- Breathlessness since 3 months
- Tiredness since 2 months

## History of Presenting Complaints

A 4-year-old boy was brought with history of headache and breathlessness. Mother told that his son used to have headache repeatedly and was relieved by paracetamol. Mother was noticing that her son used to be tired very early compared to other peers of his age. Boy used to get pain in the legs repeatedly. He often has the swelling of the face. Then the boy was shown to general practitioner for headache. Then doctor recorded the blood pressure in the

upper limb. The recording was 160/100 mm Hg. As child had associated swelling in face, doctor treated him as acute glomerulonephritis. He was given a course of procaine penicillin repeatedly. Later practitioner referred the child to the hospital for complete evaluation.

## Past History of the Patient

He was the second sibling of the nonconsanguineous marriage. He was born at full term by normal delivery. He cried immediately after delivery. There was no significant postnatal development. He was discharged on 3rd day. He was taking breast milk exclusively for 4 months. Later weaning started with cereals, fruits. He was on family food by the age of 18 months. There was no delay in developmental milestones. Of late, he was complaining of leg pain, headache and tiredness more frequently.

## CASE AT A GLANCE

### Basic Findings

Height	: 105 cm (90th centile)
Weight	: 16 kg (75th centile)
Temperature	: 38°C
Pulse rate	: 110 per minute, femoral not palpable
Respiratory rate	: 30 per minute
Blood pressure	: 160/100 mm Hg

### Positive Findings

#### History

- Headache
- Pain in legs
- Easy fatigueability

#### Examination

- Hb: 9 g/dL
- Impalpable femoral pulse
- Increased blood pressure
- Continuous murmur
- Displaced apex

#### Investigation

- X-ray chest: Large aortic arch
- ECG: Large ventricular hypertrophy
- ECHO: Normal heart with bicuspid aortic valve
- Barium swallow: Characteristic E sign

## EXAMINATION

The boy was moderately built and nourished. He was sitting quite and mild respiratory distress was present. The anthropometric measurements included, the height was 105 cm (90th centile), the weight was 16 kg (75th centile). The boy was febrile. The pulse rate was 110 per minute, femoral pulses could not be palpated. The respiratory rate was 30 per minute. The blood pressure recorded in the upper limb was 160/100 mm Hg. Blood pressure could not be recorded in the lower limb.

There was pallor. There was no clubbing and no edema. Cardiovascular system revealed, the apex beat was displaced in the left sixth intercostal space. Apex beat was forceful. Heart sounds were normal. Mid-systolic click was heard over the aortic area. Continuous murmur was audible over the midthoracic spine. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 9 g/dL
TLC	: 9,600 cells/cu mm



DLC	: $P_{70} L_{25} E_2 M_2 B_1$
ECG	: Left ventricular hypertrophy
X-ray chest	: A large aortic arch that appears like figure of three with the post-stenotic dilatation of the descending aorta
ECHO	: Normal heart with bicuspid aortic valve
Barium swallow	: Characteristic E sign
Fundoscope	: Normal

## DISCUSSION

The child has the history of headache, leg pain and easy fatigueability. High blood pressure recording in the upper limb and absence of the femoral pulse in the lower limbs give the straight diagnosis of coarctation of aorta.

Congenital coarctation of aorta is located at the junction of the aortic arch and proximal descending aorta. It is a sharp indentation involving anterior, lateral and posterior wall of the aorta. It may be distal or proximal to the ductus or ligamentum arteriosum and also to the left subclavian artery. Many affected females have Turner syndrome (45,XO).

Coarctation of aorta can be classified into preductal and postductal. Physiologically, preductal or postductal coarctation depends upon the presence or absence of the collateral anastomosing vessels.

In preductal coarctation, if there are no collaterals, the neonate becomes symptomatic immediately, i.e., hypertension resulting in left ventricular failure. Neonates who have postductal coarctation have some collaterals are spared, from developing reverse hypertension and congestive cardiac failure. The narrowed pulse pressure in descending aorta distal to the coarctation has been implicated in renal mechanism for the causation of hypertension.

If the postductal coarctation is present, it is operative in fetal life as it interferes with right ventricular output reaching the descending aorta. This stimulates formation of collaterals in the fetal life.

Obstruction stimulates growth of collateral vessels between the proximal and distal segments. The intercostal vessels enlarge and become palpable at the lower border of the ribs.

Palpable collaterals are also felt at the medial and inferior angle of the scapula. Because of the decompression of the upper segment by the collateral, the resting blood pressure in the upper extremities may be normal systolic blood pressure accentuated by the exercise.

## CLINICAL FEATURES (FIG. 1)

The symptoms may be intermittent claudication pain and weakness in the legs, and breathlessness on running.

Physical examination shows delayed and weak or impalpable femorals. Infants have equal upper and lower extremity pulses from the birth until ductus arteriosus closes (ductal patency ensures flow to the descending aorta distal to the level of obstruction).

It is usually diagnosed by a pulse blood pressure (>15 mm Hg) discrepancy between arms legs on physical examination.

### ESSENTIAL DIAGNOSTIC POINTS

- Pulse lag in lower extremities
- Blowing systolic murmur in left axilla
- Systolic blood pressure of 20 mm Hg or greater in the upper than in the lower extremities

It is important to remember that the site of coarctation does not determine whether the flow through the patent ductus arteriosus (PDA) is from left to right or from right to left. Whether the coarctation is preductal or postductal, the flow is from left to right, since the distal segment of aorta in coarctation is almost never has a mean pressure below 50 mm Hg. If there is a flow through PDA, it indicates that there is severe pulmonary arterial hypertension.

It presents with heart failure in early infancy. It may be detected in evaluation of hypertension and murmur. Associated cardiac deformities may be VSD, PDA or aortic valve lesion.

The heart size remains normal with left ventricular forcibly heaving apical impulse. Systolic thrill may be present in the suprasternal notch.

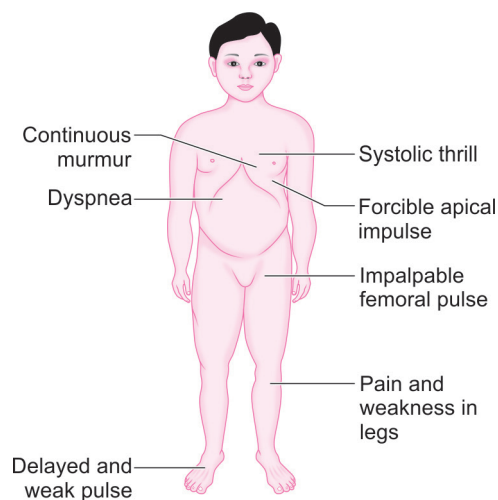


Fig. 1: Clinical features.

The first sound is accentuated and followed by loud constant ejection click. The second sound is normally split with loud aortic component. Ejection systolic murmur is heard maximally over back in interscapular region. The murmur starts late in systole and may appear to go through second sound suggesting continuous murmur. Continuous murmur may be heard over the collaterals in the chest wall. An aortic ejection systolic murmur and/or an aortic regurgitant murmur may also be present because of bicuspid aortic valve.

**ECG:** It shows left ventricular hypertrophy. It shows right ventricular hypertrophy infants with severe coarctation because RV serves as systemic ventricle during fetal life.

**Radiograph:** It shows normal sized heart or some degree left ventricular enlargement. The aorta proximal to coarctation is prominent. The aortic outline may indent. The poststenotic segment is often dilated. This combination of abnormalities results “the figure of 3” on chest radiograph. Notching of ribs caused marked enlargement intercostal collaterals can be seen.

**Echocardiography:** Two-dimensional ECHO and color flow Doppler are used to visualize coarctation directly and continuous wave Doppler estimates the degree coarctation. Diastolic run-off flow is detected by continuous wave Doppler, if obstruction is significant.

**Barium swallow:** It shows characteristic E-sign and confirms the duration of coarctation. The characteristic notching of the lower ribs tends to appear beyond the age of 10 years.

#### GENERAL FEATURES

- Heart failure
- Hypertension
- Headache

#### LABORATORY SALIENT FINDINGS

- ECG shows left ventricular hypertrophy
- Radiograph shows normal-sized heart with prominent ascending aorta and the aortic knuckle
- Barium swallow shows characteristic E-sign and confirms the duration of coarctation
- The characteristic notching of the lower ribs tends to appear beyond the age of 10 years
- **ECHO:** The gradient across the narrowing is obtained with Doppler

## COMPLICATIONS

The degree of systemic hypertension determines the severity of coarctation. Cardiac enlargement indicates left ventricular failure and severe coarctation. Complications include severe neurological damage and even deaths because of associated cerebrovascular disease. Subarchnoid or intracerebral hemorrhage may result from the rupture of berry aneurysm. Abnormalities of the subclavian artery may occur. Other serious problems encountered are systemic hypertension, congestive cardiac failure (CCF), dissection of aorta and aneurysm of aorta.

## TREATMENT

Infants with coarctation of aorta may present in extremes secondary to LV dysfunction and low cardiac output. Resuscitative measures include PGE<sub>2</sub> infusion (0.05–0.1 µg/kg/min) to reopen ductus.

Medical management includes control of congestive cardiac failure in infancy. The patients can be operated at any age. But the risk of operation is low if it is done between the ages of 1 and 10 years. Ideally the patients should be operated as early as possible after the age of 1 year.

Systemic hypertension may persist following operation. Coarctation is amenable to treatment by balloon angioplasty in patients with LV function. Balloon angioplasty is being increasingly utilized for the relief of recoarctation as well as primary mode of treatment in place of operative treatment.

## COURSE PROGNOSIS

Children with coarctation corrected after age of 5 years are at increased risk for systemic hypertension and myocardial dysfunction.

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# Infective Endocarditis

## PRESENTING COMPLAINTS

A 4-year-old boy was brought with the complaints of:

- Fever since 7 days
- Pain in abdomen since 4 days
- Vomiting since 2 days
- Tiredness since 2 days

## History of the Presenting Complaints

A 4-year-old boy was brought with the history of high-grade fever and tiredness. He was accompanied by his mother. Mother told that her son had fever since the past 1 week. To begin with it was moderate degree. She took her son to the general practitioner. Doctor had prescribed symptomatic treatment. Later fever increased in intensity and

used to be continuous associated with chills and rigors. Later mother also gave the history of vomiting and pain abdomen.

Mother revealed the history of heart murmur in her son. She showed all the reports pertaining to the cardiac problem as it was diagnosed at birth.

## Past History of the Patient

He was the only sibling of the nonconsanguineous marriage. He was born at term by normal vaginal delivery. He cried immediately after the delivery. Cry of the baby was good. Pediatrician who attended the delivery revealed the presence of congenital heart disease and advised the parents to attend cardiac clinic later on. In the postnatal ward, he was taking breast milk. Weaning was started as per the advice of the family doctor. All the developmental milestones were normal. His academic performance in the school was good. But he never used to take part in sports.

In the cardiac clinic, he was diagnosed to have VSD and was advised symptomatic treatment till the boy was 7 years old.

## EXAMINATION

Boy was moderately built and nourished. Child was looking toxic and dehydrated. His anthropometric measurements included the height 99 cm (50th centile) and weight was 14 kg (50th centile).

He was febrile, i.e., 39°C. His pulse rate was 120 per minute. The respiratory rate was 30 per minute. The blood pressure recorded was 70/50 mm Hg. There was pallor and clubbing. There was no edema and lymphadenopathy.

Cardiovascular system examination revealed the displacement of apex beat to the anterior axillary line. Systolic thrill was felt to the left lower sternal edge. On auscultation, the pulmonary component of the second sound was loud. There was pansystolic murmur heard over the left 3rd and 4th intercostals space.

Per-abdomen examination showed the presence of splenomegaly 2 mL below the costal margin. It was nontender and soft.

### CASE AT A GLANCE

#### Basic Findings

Height	: 99 cm (50th centile)
Weight	: 14 kg (50th centile)
Temperature	: 39°C
Pulse rate	: 120 per minute
Respiratory rate	: 30 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Fever
- Vomiting
- Murmur at birth
- Known case of VSD

##### Examination

- Pallor
- Febrile
- Systolic thrill
- Systolic murmur
- Splenomegaly

##### Investigation

- Hb: 9 g/dL
- TLC: Increased
- Urine: Microscopic hematuria
- ECG: Biventricular hypertrophy
- Chest X-ray: Enlarged heart with pulmonary plethora, left atrial enlargement

## INVESTIGATION

Hemoglobin	: 9 g/dL
TLC	: 20,800 cells/cu mm
DLC	: P <sub>70</sub> L <sub>28</sub> E <sub>2</sub>
ESR	: 38 mm in the 1st hour
Urine routine	: 8–10 RBCs/HPF
Blood culture and sensitivity	: Sterile
Urine culture and sensitivity	: Sterile
ECG	: Biventricular hypertrophy
Chest X-ray	: Enlarged heart with pulmonary plethora and left atrial enlargement

## DISCUSSION

A known case of rheumatic heart disease developed the high temperature associated with chills and rigors. This was associated with the clinical findings of the pallor, splenomegaly and laboratory findings of microscopic hematuria suggests infective endocarditis (IE).

Infective endocarditis in pediatric patients is rare (5–12 per 100,000 pediatric admissions) and often associated with an underlying congenital heart defect or, increasingly, central indwelling intravascular catheters. However, structurally normal hearts may also be infected. Premature infants now account for 10% of pediatrics.

The clinical presentation of IE in children does not follow the classical presentation described in adults. Fever is the most common finding and may be associated with changing murmur and nonspecific symptoms. The primary site of infection, defense mechanisms of the host and organism determine the clinical manifestations and rate of progression. IE can involve native or prosthetic cardiac valves, septal defects, mural endocardium, patent ductus arteriosus (PDA), or intravascular devices such as catheters, occlusion devices, patches, and surgically constructed shunts. Blood cultures and echocardiography are of paramount importance to aid in the diagnosis.

Infective endocarditis is an infection of the endocardial lining of the heart, includes acute and subacute bacterial endocarditis, as well as nonbacterial endocarditis caused by viruses, fungi, and other microbiologic agents. It is a significant cause of morbidity and mortality in children and adolescents despite advances in the management and prophylaxis of the disease with antimicrobial agents. The disease represents a complex interplay between a pathogen and host factors such

as endothelial disruption and immune function that is still not completely understood; the nature of the infecting organism has changed over time; diagnosis may be difficult during early stages and is thus often delayed until a more serious infection has set in.

It is often a complication of the congenital or rheumatic heart disease. It can also occur without any cardiac malformation. Rheumatic heart disease accounts for 60%. The common valves involved are mitral valve and aortic valves.

The infections which predisposes are urinary tract infection, osteomyelitis, ear infection and tooth abscess. Important risk factors are open heart surgery and prosthetic valves. Procedures such as tonsillectomy, rigid bronchoscopy, endoscopic biopsy, barium enema, percutaneous liver biopsy and genitourinary procedure are predisposing factors.

Previously *Streptococcus viridans* was the agent most commonly responsible in pediatric age groups. Now the *Staphylococcus aureus* leads the list. Staphylococcal endocarditis is more common in patients with no underlying heart diseases. *Streptococcus viridans* is more common after lower bowel or genitourinary disease. Fungal organisms are more common with open heart surgery.

Congenital heart disease accounts for 25%. The common congenital heart diseases are ventilator septal defect (VSD), PDA, tetralogy of Fallot (TOF), MVP, bicuspid aortic valve and coarctation of aorta. Dental procedures and poor oral hygiene are important predisposing factors.

In patients with congenital heart disease, a high velocity of blood is ejected through a hole or stenotic orifice which are more susceptible for endocarditis. Vegetations are mainly formed at the site of endocardial or frictional erosion, that results from the turbulent flow.

Children with the ventilator septal defect (VSD), left side valvular disease and systemic pulmonary arterial communication including palliative shunts are at higher risk. Thus, tetralogy of Fallot, VSD, aortic stenosis, patent ductus arteriosus, transportation of great arteries, Blalock-Taussig shunts are the most frequent structural lesions associated with endocarditis. In older patients, congenital bicuspid aortic valve and mitral valve prolapse (MVP) pose additional risk for endocarditis.

In older patients, congenital bicuspid aortic valves and MVP with regurgitation pose additional risks for endocarditis. Surgical correction of congenital heart disease may reduce but does not eliminate the risk of endocarditis with the

exception of repair of a simple atrial septal defect or patent ductus arteriosus without prosthetic material.

## **PATHOGENESIS**

Two factors are important in the pathogenesis of IE, the presence of structural abnormality of the heart or great arteries and bacteremia. The shear force associated with an abnormal high velocity jet stream of blood due to a structural heart defect or trauma produced by an indwelling catheter in heart damage the endothelium.

Infective endocarditis is established by the interaction of a bloodstream pathogen with damaged endocardium. Intact endothelium is a poor stimulator of coagulation and is resistant to colonization by microorganisms; however, damaged endothelium is a potent inducer of thrombogenesis and provides a nidus to which bacteria adhere. Turbulent flow produced by certain congenital or acquired heart diseases causes shear stress and damages the endothelium.

Thrombogenesis ensues and results in the deposition of sterile clumps of platelets, fibrin, and the formation of nonbacterial thrombotic endocarditis (NBTE). NBTE may also be produced in structurally normal hearts when indwelling intravenous catheters damage the endocardium or valvar endothelium. NBTE can then be converted to an infected vegetation in a patient with transient bacteremia or fungemia. Activities of daily living such as chewing toothbrushing, and flossing, account for most bloodstream seeding of an NBTE.

Bacteremia may also be caused by entry of organisms at the site of entry of percutaneous catheters, via the catheter lumen, or as a result of direct infection of an indwelling device at the time of placement. Bacteremia, however, does not invariably produce IE. The propensity to adhere to an NBTE depends on the type of microorganism. Gram-positive microorganisms are most commonly responsible for IE in children because they possess specific surface components that facilitate adherence.

Establishment of IE results from the interaction of several host and microbial factors. Following endocardial damage, bacterial access to the bloodstream from elsewhere and subsequent adherence to endocardial surfaces are required for the establishment of IE. It is now thought that the great majority of IE develops as the result of transient bacteremia related to activities of daily life, but not all bacteria are capable of initiating this process. The endocardium appears to be a

preferential site of microbial adherence and may have some specificity for binding with certain bacteria. The presence of several factors, including bacterial adhesions, endothelial-binding proteins, and agglutinating antibodies that clump bacteria, promotes adherence of organisms to damaged endocardial surfaces. The venturi effect (the reduction in fluid pressure that results when blood flows through a constricted area) deposits bacterial colonies immediately beyond the orifice that separates high- and low-pressure areas.

Classically, viridians streptococci have been the most common cause of IE, progressing along a subacute course in patients with preexisting cardiac lesions in which fever, fatigue, and immune complex-mediated clinical manifestations develop slowly over weeks or months. Enterococci behave in a fashion similar to the viridans streptococci. IE caused by *Staphylococcus aureus* has historically followed an acute course with rapid progression and poor outcome, including death, often in patients with normal hearts. Prosthetic heart valves within 2 months after implantation are prone to infection with coagulase-negative staphylococci and *S. aureus*, as are neonates who require intensive care and intracardiac central lines.

Those organisms (*Haemophilus aphrophilus*, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) that normally inhabit the upper respiratory tract are often associated with IE when recovered from the bloodstream. Anaerobic and microaerophilic bacteria and polymicrobial infections are responsible for a minority of cases of IE.

The most common pathogens in neonates are *Staphylococcus aureus*, coagulase-negative staphylococci (CONS) gram-negative bacterial species, and *Candida* species. After the 1st year of life, viridians group streptococci (VGS, e.g., *Streptococcus sanguis*, *Streptococcus mitis* group, *Streptococcus mutans*) and *S. aureus* are the most frequently isolated organisms in patients with underlying CHD. Importantly, *S. aureus* is the most common cause of acute (rapidly progressive) IE. Coagulase-negative staphylococci (CONS) are also a frequent cause of IE and can cause infection in both native and prosthetic valves, indwelling vascular catheters, and prosthetic materials. *Enterococcus* IE occurs much less frequently in children than in adults. Gram-negative organisms cause <10% of IE in children and include the HACEK (*Haemophilus* species, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella* species) organisms.



The prevalence of culture-negative endocarditis (CNE) is approximately 5–10%; the most common causes are recent or current antibiotic therapy or infection caused by a fastidious organism such as *Bartonella*, *Tropheryma whippelii*, *Coxiella burnetii* (Q fever), or *Brucella*.

## Organisms

Most organisms that cause IE are gram-positive cocci including viridians group, streptococci, staphylococci and enterococci. These organisms account for 90% cases.

### Gram-positive Cocci

- Viridians group
- Enterococci
- Staphylococci
- Other streptococci
- *St. faecalis*, *St. Pyogenes*, *Pneumococcus*, anaerobic and microaerophilic streptococci

### Gram-positive Bacilli

- *Listeria monocytogenes*
- *Bacillus subtilis*
- *Diphtheroids*
- *Nocardia israeli*

### Gram-negative Organisms

- *Pseudomonas*
- *Neisseria gonorrhoeae*
- *E. coli*
- *Klebsiella*
- *Enterobacter*

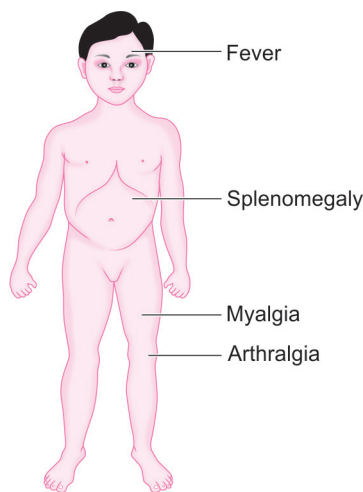
### Yeast and Fungi

*Candida* sp.

## CLINICAL FEATURES (FIG. 1)

Early manifestations are usually mild, especially when viridans group streptococci are the infecting organisms. Prolonged fever without other manifestations (except, occasionally, weight loss) persisting for several months may be the only symptom. Alternatively, the onset may be acute and severe, with high, intermittent fever and prostration.

It is a multisystemic disease with various manifestations. Any fever in a patient with known cardiac disease should arouse the suspicion of IE in the presence of classical syndrome of fever, anemia, murmur and embolic phenomenon. Infective endocarditis becomes a diagnostic consideration.



**Fig. 1:** Clinical features.

Clinical manifestations in newborn are nonspecific. They are indistinguishable from septicemia or congestive cardiac failure. These neonates have feeding difficulties, respiratory distress and tachycardia. They have a new or changing heart murmur and hypotension. The neurological signs and symptoms such as seizures, hemiparesis and apnea are present.

Usually, the onset and course vary between these two extremes. The symptoms are often nonspecific and consist of low-grade fever with afternoon elevations, fatigue, myalgia, arthralgia, headache, and, at times, chills, nausea, and vomiting. New or changing heart murmurs are common, particularly with associated heart failure. Splenomegaly and petechiae are relatively common.

*Prolonged fever* is the single most common manifestation (90%). The fever fluctuates between 101–103°F. Onset of fever may be acute and severe, with high intermittent fever and prostration. Fever will be associated with fatigue, myalgia, arthralgia, headache and at times chills, nausea and vomiting.

The physical examination is highly variable due to possible structural changes at the local infection site, embolization from vegetations to distant organs, and circulating immune complexes. Serial auscultation is crucial because it may be difficult to appreciate changes in a patient with a pre-existing murmur. A new or evolving valvar lesion may cause leaflet destruction, resulting in a new or louder murmur or gallop due to congestive heart failure. Alternatively, attenuation of a continuous murmur or decrease



in oxygen saturation in a cyanotic child with a prosthetic systemic to pulmonary shunt may reflect obstruction to flow due to graft infection heart rate and rhythm must also be closely monitored because heart block may be a sign of a life-threatening complication.

*Cardiac murmur* is almost universal. The appearance of the new murmur and an increase in the intensity of existing murmur are important.

Splenomegaly is seen in 25–60% of cases. It is due to reticuloendothelial proliferation caused by chronic stimulation from the bacteremia and circulating immune complexes. Splenomegaly may be absent in acute cases.

The *classical skin manifestations* develop late in the course of the disease. These manifestation include:

*Osler nodes* are tender, penalized intradermal nodule in the pads of the fingers and toes.

*Janeway lesions* are painless small erythematous or hemorrhagic lesions on the palms and soles.

*Splinter hemorrhages* are seen as linear lesions beneath the nails. These lesions represent vasculitis produced by circulating antigen-antibody complexes.

*Embolic Phenomenon:* These are seen in 50% of cases. Embolization from the tricuspid valve may cause septic pulmonary emboli, resulting in breathlessness and scattered, fluffy infiltrates on chest radiographs.

Pulmonary emboli are seen in patients with VSD, PDA and systemic PA shunt. In 20% CNS, embolization is seen and results in seizure and hemiparesis. CNS complications are more common with left-sided defects such as aortic and mitral valve disease and cyanotic heart diseases. Renal embolization results in hematuria and renal failure.

Complications are often due to systemic embolization of a vegetation. Although embolic events can occur late, the majority occur in the first 2–3 weeks after diagnosis and initiation of therapy. Embolization is most commonly due to fungal or *S. aureus* infection.

Serious neurologic complications such as embolic strokes, cerebral abscesses, mycotic aneurysms, and hemorrhage are most often associated staphylococcal disease and may be late manifestations. Meniscus, increased intracranial pressure, altered sensorium, and focal neurologic signs are manifestations of these complications.

Myocardial abscesses may occur with staphylococcal disease and may damage the cardiac

conducting system, causing heart block, or may rupture into pericardium and produce purulent pericarditis. Pulmonary and other systemic emboli are infrequent, except with fungal disease. Many of the classic skin findings develop late in the course of the disease, they are seldom seen in appropriately treated patients. Clubbing of finger can occur rarely in most chronic cases.

#### ESSENTIAL DIAGNOSTIC POINTS

- Pre-existing organic heart disease
- Persistent fever
- Splenomegaly
- Leukocytosis
- Elevated ESR
- Hematuria
- Positive blood culture
- Embolic phenomena

#### GENERAL FEATURES

- Anemia
- Hematuria
- Osler node
- Janeway lesion
- Splinter hemorrhage

## DIAGNOSIS

### Blood Culture

It is the mainstay of diagnosis of IE. It is indicated for all patients with the fever of unexplained origin, history of heart disease or previous endocarditis. Three samples of sufficient amount of blood, i.e., 1–3 mL in infants and young children and 5–7 mL in older children is optimal. It is collected with aseptic precautions every half an hour from different sites on the 1st day, and if there is no growth by 2nd day.

If there is no growth by 2nd day of incubation, two more samples may be obtained. In patients, who are not acutely ill and whose blood culture is still negative, the antibiotics may be withheld for 48 hours or longer, while additional blood culture is obtained.

Of three blood cultures, one should be for anerobic culture. Three cultures can detect over 95% cases. Blood culture is negative in almost 50% cases. Most important causes for negative blood culture are prior antibiotics, anerobic organism and fungal infection.

The critical information for appropriate treatment of IE is obtained from blood cultures. Blood specimens for culture should be obtained as promptly as possible, even if the child feels well and has no other physical findings.

In 90% of cases of endocarditis, the causative agent is recovered from the first two blood cultures. Others specimens that may be cultured include scrapings from cutaneous lesions, urine, synovial fluid, abscesses and, in the presence of manifestations of meningitis, the cerebrospinal fluid.

The microbiology laboratory and infectious disease specialist should be consulted in all suspected cases of IE. The laboratory will need to incubate cultures for of least 2 weeks if fastidious or unusual organisms are suspected, Serologies and molecular techniques, such as polymerase chain reaction, may help to identify fastidious organisms, and cell cultures may help identify intracellular organisms such as *Bartonella* or *Coxiella*. In patients who undergo surgery for IE, resected cardiac tissue is helpful as well. Several additional but nonspecific laboratory tests may help support the diagnosis. Patients often have elevated acute-phase reactants, anemia (due to hemolysis or chronic disease), and microscopic hematuria or proteinuria, leukocytosis is generally inconsistent, but patients may have a left shift. IE is diagnosed if a patient has clinical and/or echocardiographic evidence of IE but blood cultures are repeatedly negative. Conversely, positive blood culture in a child with CHD or a history of previous IE does not necessarily indicate IE.

## Hematological

Anemia is seen in 50–80% cases. Usually normocytic and normochromic type of anemia is seen. It is due to hemolysis or anemia of chronic disease. Leukocytosis is present. Thrombocytopenia is unusual. It may be seen with patients with splenomegaly or DIC. Erythrocyte sedimentation rate (ESR) is almost always elevated. It may be normal in patients with CCF.

## Urine

Microscopic hematuria and proteinuria are present. They reflect immune complex injury. Renal infection may cause gross hematuria. Glomerulonephritis can cause hematuria, pyuria and cellular casts.

There may be increase in gamma-globulin, positive-rheumatoid factor, presence of cryoglobulin, low complement levels and circulatory immune complex. Antibodies against the causative organism may be increased.

According to the Duke criteria, definite IE must meet two major criteria, or one major and three minor criteria, or five minor criteria. Major criteria

are: (1) multiple positive blood cultures, for typical IE organisms, and (2) evidence of endocardial involvement either by echocardiography or by the development of a new regurgitant murmur. Minor criteria are a predisposition to IE (e.g., CND), fever, vascular phenomena, immunologic phenomena and microbiologic or serologic evidence that does not meet major criteria. Each of the major and minor criteria has qualifying details. Modified Duke criteria may be less specific in children than adults.

Nonspecific acute-phase reactants, such as ESR, C-reactive protein and rheumatoid factor are usually elevated; the tests may also be useful in following the progress of therapy.

Two-dimensional echocardiography is the principal modality for detecting vegetations. Typical echocardiographic findings include the presence of a vegetation, abscess, and new or worsening valvar insufficiency. Children have superior echocardiographic windows compared to adults, and transthoracic echocardiography (TTE) has an excellent reported sensitivity (81–97%) for detecting vegetations. Transesophageal echocardiography (EP) is more invasive, more expensive, and generally unnecessary in most pediatric cases.

### LABORATORY SALIENT FINDINGS

- Blood culture
- Anemia, leukocytosis, thrombocytopenia
- Microscopic hematuria and proteinuria are present
- Increase in gamma-globulin
- Positive rheumatoid factor
- Presence of cryoglobulin
- Low complement levels and circulatory immune complex

## COMPLICATIONS

- Congestive heart failure
- Embolism, e.g., cerebral, pulmonary, renal, coronary
- Periannular extension of abscess
- Arrhythmia development, new heart block
- Prosthetic device dysfunction
- Valvular dehiscence
- Graft or shunt occlusion
- Persistent bacteremia or fungemia
- Metastatic infection
- Mycotic aneurysms
- Glomerulonephritis/renal failure

## TREATMENT

It is a medical emergency because it can damage valves, the myocardium and other parts of the

body like brain and the kidney. Hence, early and effective treatment will certainly prevent the morbidity and mortality of the patient.

Management requires a multidisciplinary team consisting of a pediatric cardiologist, infectious disease specialist, cardiothoracic surgeon, and general pediatrician. Empiric antibiotic treatment in a child with CHD with fever alone should be discouraged. For cases of suspected or confirmed IE, a prolonged course of bactericidal intravenous antibiotics is given for 4–8 weeks, in patients who are not acutely ill. Antibiotics may be withheld while additional cultures are obtained. The choices of antibiotics and duration of therapy are determined by the specific pathogen, site of infection, underlying anatomy, and presence of prosthetic material. Serum concentrations of vancomycin and aminoglycosides should be monitored to achieve therapeutic levels and prevent potential side effects such as nephrotoxicity and ototoxicity.

The treatment of IE includes the treatment of the current episode and prevention of endocarditis. Antibiotics remain the mainstay of treatment. Choice of antibiotics depends on the organism isolated by blood culture. An empiric broad-spectrum antibiotics should be used when the culture is negative. Bactericidal antibiotics are used to prevent or reduce the possibility of treatment failure and relapse.

Some basic considerations apply in determining therapy for IE. High doses of parenteral antibiotics are required to exceed the bactericidal concentration for the infecting organism, and synergistic combinations are recommended in some situations (e.g., enterococci) to improve effectiveness or to shorten duration of treatment.

Oral antibiotics are insufficient unless bioavailability approaches 100%. Antibiotics used should be bactericidal rather than bacteriostatic, because the relatively avascular vegetations of IE offer little access to host defenses. Pediatric and adult guidelines for therapy of specific pathogens are based on susceptibility testing and the presence or absence of prosthetic material.

Beta-lactams (including penicillins and cephalosporins) and vancomycin are used most frequently. Gentamicin is commonly added for a period that time to achieve synergy with B-lactam or vancomycin, especially when enterococci or *S. aureus* is the causative organism. Rifampicin is useful as an adjunct when *S. aureus* infects prosthetic valves.

Antibiotic therapy should be started immediately after the diagnosis. When the virulent organism is responsible delay in the treatment, may

result is progressive endocardial damage. This is associated with likelihood of severe complications.

Depending upon the clinical and laboratory responses, antibiotic therapy may require modification and sometimes more prolonged treatment may be recommended. In case of non-*Staphylococcus*, bacteremia usually resolves in 24 hours; the fever resolves in 5–6 days. Resolution in staphylococcal disease takes longer time.

**DRUG DOSES IN ENDOCARDITIS (ALL ARE GIVEN INTRAVENOUSLY AND DIVIDED INTO 2–4 DOSES/DAY EXCEPT STREPTOMYCIN GIVEN AS IM)**

Penicillin G	10–20 million U/day	4 doses/day
Cefazolin	60 mg/kg/day	3 doses/day
Streptomycin	40 mg/kg/day (IM)	Once daily
Gentamicin	7.5 mg/kg/day	2 doses/day
Amikacin	30 mg/kg/day	3 doses/day
Ampicillin	400 mg/kg day	4 doses/day
Cloxacillin	200 mg/kg/day	3 doses /day
Carbenicillin	400 mg/kg/ day	4 doses/day
Vancomycin	60 mg/kg/day	2–3 doses/day

Bacteremia generally resolves within few days after the appropriate therapy. Blood culture should be repeated to assess the adequacy of treatment and document cessation of bacteremia. Additional blood culture should be performed once or twice in 8 weeks after complication of antibiotics to ensure the complete cure.

Blood cultures should be obtained daily until bacteremia resolves; this usually occurs within several days of appropriate treatment. The efficacy of antimicrobial therapy is indicated by the disappearance of fever, sterilization of blood cultures, and normalization of inflammatory markers, clinical and biologic surveillance (including occasional repeat blood cultures) should continue in the subsequent 6–8 weeks after completion of therapy when the risk of relapse is highest. A follow-up echocardiogram should also be performed to establish a new baseline. In most cases, this is all that is required to cure the infection and prevent life-threatening complications. However, there are cases where cardiovascular surgery may be necessary and lifesaving.

A prolonged course of therapy, i.e., at least 1 week, often 4–8 weeks is necessary because organism embedded within fibrin-plated matrix and exist in very high concentration with relatively low rates of decrease susceptibility to beta-lactam and other cell wall active antibiotics.

TREATMENT OF INFECTIVE ENDOCARDITIS				
<i>Etiologic agent</i>	<i>Drug</i>	<i>Dose</i>	<i>Route</i>	<i>Duration of therapy (week)</i>
<i>Streptococcus viridans</i> , <i>S. bovis</i> [minimal inhibitory concentration (MIC) $\leq 0.1$ $\mu\text{g/mL}$ ]	1. Penicillin G or 2. Penicillin G plus gentamicin	200,000–300,000 U/kg/24 h not to exceed	IV	4–6
		20 million U/24 h As above No.1	IV	2–4
		3–7.5 mg/kg/h q8h not to exceed 240 mg/24 h	IV	2
<i>S. viridans</i> , <i>S. bovis</i> (MIC $\geq 0.1$ $\mu\text{g/mL}$ )	3. Penicillin G plus gentamicin	As above No. 2	IV	4–6
		As above no. 2	IV	2
<i>S. viridans</i> or enterococci ( <i>S. bovis</i> or <i>S. faecalis</i> ) (MIC $> 0.5$ $\mu\text{g/mL}$ )	4. Penicillin G Or Ampicillin Plus Gentamicin	As above No. 2	IV	4–6
		300 mg/kg/24 h q4–6h not to exceed	IV	4–6
		12 g/24 h As above No. 2	IV	4–6
<i>S. viridans</i> , <i>S. bovis</i> (penicillin allergy)	5. Vancomycin plus 6. Gentamicin if resistant	40–60 mg/kg/24 h q8–12h not to exceed	IV	4–6
		2 g/24 h As above No. 2	IV	4–6
<i>Staphylococcus aureus</i>	7. Nafcillin or oxacillin plus optional gentamicin	200 mg/kg/24 h q4–6h not to exceed	IV	6–8
		12 g/24 h As above No. 2	IV	1–2
<i>S. aureus</i> (methicillin-resistant) (penicillin allergy)	8. Vancomycin plus optional trimethoprim sulfamethoxazole	As above No. 5 12 mg/kg/24 h trimethoprim q8h not to exceed 1 g/24 h	IV IV, PO	6–8 4–8
<i>S. aureus</i> (with prosthetic device, methicillin-sensitive)	9. Nafcillin plus gentamicin plus optional rifampicin	As above No. 7	IV	6–8
		As above No. 2	IV	2
		10–20 mg/kg/24 h q12h not to exceed 600 mg/24 h	PO	$\geq 6$
<i>S. aureus</i> (with prosthetic device, methicillin-resistant)	10. Vancomycin plus gentamicin plus optional rifampicin	As above No. 5	IV	6–8
		As above No. 9	IV	2
		As above No. 9	PO	$\geq 6$
<i>S. epidermidis</i>	11. Vancomycin plus optional rifampicin	As above No. 5	IV	6–8
		As above No. 9	PO	6–8
<i>Haemophilus</i> species	12. Ampicillin plus optional gentamicin	As above No. 4	IV	4–6
		As above No. 2	IV	2–4
Unknown postoperative	13. Vancomycin plus gentamicin	As above No. 5	IV	6–8
		As above No. 2	IV	2–4
Nonoperative	14. Nafcillin Or Vancomycin plus gentamicin plus optional ampicillin	As above No. 7	IV	6–8
		As above No. 5	IV	6–8
		As above No. 2	IV	2–4
		As above No. 4	IV	6–8

Outpatient treatment can be considered in select patients after initial inpatient management. These patients must be hemodynamically stable, afebrile, have negative blood cultures, and not be at high risk for complications. There

should be easy access to a hospital for prompt re-evaluation should complications develop. Frequent monitoring by a home health nurse who can assess adherence to drug therapy is also essential.

Digitalis, salt restriction and diuretic therapy should be used for the treatment of heart failure. Surgical intervention is indicated for severe aortic or mitral valve involvement with intractable heart failure. A mycotic aneurysm, rupture of an aortic sinus or dehiscence of an intracardiac patch requires an emergency operation.

Fungal endocarditis is difficult to manage. It has a poor prognosis regardless of treatment. It is commonly seen after the cardiac surgery especially in severely debilitated or immunosuppressed patients. The drugs of choice are amphotericin B and 5-flucytosine. Infected tissue is excised usually with the limited success.

### ECHOCARDIOGRAPHIC FEATURES SUGGESTING FOR SURGICAL INTERVENTION

- Vegetation
- Persistent vegetation after systemic embolization
- Anterior mitral leaflet vegetation, particularly >10 mm
  - >2 embolic events during or after antimicrobial therapy
  - >1 embolic event during the first 2 weeks of antimicrobial therapy
- Increase in vegetation size despite appropriate antimicrobial therapy
- Valvular dysfunction
- Valve perforation or rupture
- Heart failure unresponsive to medical therapy
- Acute mitral or aortic regurgitation with signs of ventricular failure
- Perivalvular extension
- New heart block
- Large abscess or extension of abscess despite of appropriate antimicrobial therapy
- Valvular dehiscence, rupture, or fistula

Most children with IE are cured with antibiotic therapy and occasionally surgical management. However, overall inpatient mortality remains at least 5–10%. This rate is even higher in premature infants and patients with IE caused by *S. aureus*. Specific types of CHD are also associated with poorer outcomes. Children who survive an episode of IE are at increased risk for relapse and thus must be followed closely and educated to report occurrence of fever. The pediatrician therefore plays a critical role in surveillance.

Surgical intervention, in addition to medical therapy, is generally indicated in fungal IE, when bacteremia persists despite appropriate antibiotic therapy, when congestive heart failure is uncontrolled by medical therapy, or in the presence of any of the following abscess of the valve annulus

or the myocardium, systemic, embolic events, rupture of a valve leaflet or chordae, or acute valve insufficiency with cardiac failure. Prosthetic valve endocarditis per se is not an indication for surgery, but early surgical intervention may improve the outcome.

The most frequent complications of IE are congestive heart failure and arterial embolization. Intracardiac lesions that may lead to congestive heart failure include valvar insufficiency caused directly by vegetations or by chordal rupture, abscesses or the myocardium or valvar annulus, myocardial infarction, and conduction defects. Arterial emboli occur most frequently when large (<10 mm) mobile vegetations develop on valves, particularly the anterior leaflet of the mitral valve. Although vegetations slowly regress with effective therapy, sudden disappearance of vegetation should raise the possibility of embolization.

Emboli originating from left-sided vegetations can affect vascular beds in the systemic or cerebral circulation, whereas right-sided lesions produce pulmonary emboli. Cerebral emboli occur in 30% of left-sided IE and are mostly clinically silent. Magnetic resonance imaging (MRI) is often considered for detection. Mycotic aneurysms most commonly occur at vessel bifurcations and can involve any artery. Intracranial mycotic aneurysms often require surgery.

### PREVENTION

Prevention of IE is more important than the diagnosis and treatment. Certain patient population with high-risk is identified. Cardiac conditions have been stratified into high, moderate and negligible risk on the basis of risk of developing endocarditis and its severity. Prophylaxis is recommended for those in high- and moderate-risk categories.

The prophylactic administration of antibiotics prior to dental procedures has been routine for over 50 years. While guidelines have continued to evolve, published data have failed to prove the effectiveness of antibiotic prophylaxis to prevent IE. There is consistent scientific evidence to suggest that dental procedures are a rare cause of IE, and prophylactic antibiotics prior to such procedures may prevent an exceedingly small number of cases. On the contrary, bacteremia from activities of daily living far exceeds that of dental procedures and is therefore much more likely to cause IE. This has resulted in a significant shift in prevention strategies toward a greater emphasis on oral hygiene and access to dental care for children with CHD. This emphasizes the necessary role the



pediatrician to stress the importance of good oral hygiene, prevention of gingival and dental disease, and access to routine dental care for children at risk for IE.

Prophylaxis is now only recommended for children with a prosthetic valve or prosthetic material, certain types of CHD (unrepaired cyanotic CHD, repaired CHD with prosthetic material or device during the first 6 months after the procedure, and repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device), or a previous case of IE. It is also recommended in heart transplant recipients with cardiac valvulopathy. Prophylaxis consists of a single dose of amoxicillin (50 mg/kg; maximum, 2 g), 30–60 minutes prior to all dental procedures that involve manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa.

### Standard Prophylaxis

Oral amoxicillin 50 mg/kg orally 1 hour before procedure and then half the dose 6 hours after the initial dose.

If allergic to penicillin, ampicillin or amoxicillin.

- Erythromycin 20 mg/kg orally 2 hours before procedure and half a dose 6 hours after initial dose, or
- Clindamycin 10 mg/kg orally 1 hour before procedure and then half the dose 6 hours after initial dose.

### In Patients Unable to Take Oral Medication

Ampicillin 50 mg/kg IV/IM 30 minutes before the procedure, and then half the dose 6 hours after

the initial dose is recommended. In patients allergic to penicillin alternatively clindamycin 10 mg IV/IM 30 minutes before the procedure and half the dose IV or oral 6 hours after the initial dose.

### High-risk Patients

Ampicillin 50 mg/kg and gentamycin 2 mg/kg IV/IM 30 minutes before the procedure followed by amoxicillin 25 mg/kg orally 6 hours after the initial dose or IV/IM can be repeated 8 hours later.

In high-risk patients allergic to penicillin vancomycin 20 mg/kg IV over 1 hour started 1 hour before the procedure. No repeat dose is needed.

Antimicrobial and prophylaxis prior to various procedures, including dental cleaning and other forms of dental manipulation, reduces the incidence of IE in susceptible patients.

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# Patent Ductus Arteriosus

## PRESENTING COMPLAINTS

A 6-month-old boy was brought with the complaints of:

- Not gaining weight since 6 months
- Repeated cough and cold since 3 months

## History of Presenting Complaints

A 6-month-old boy was brought to the pediatric outpatient department with history of not gaining weight. Boy used to get repeated respiratory tract infection over the last 3 months. Each time he was treated with full course of the antibiotics. His other developmental milestones were normal.

## Past History of the Patient

He was the first sibling of nonconsanguineous marriage. He was delivered at full term, and delivered normally. He cried immediately after delivery. Cry of the baby was normal. The Apgar score at 1 minute was 8/10 and at 5 minutes was 10/10. The birth weight was 2.8 kg. The length was 49 cm.

### CASE AT A GLANCE

#### Basic Findings

Length	: 64 cm (50th centile)
Weight	: 5 kg (3rd centile)
Temperature	: 37°C
Pulse rate	: 126 per minute, bounding
Respiratory rate	: 26 per minute
Blood pressure	: 60/30 wide pulse pressure

#### Positive Findings

##### History

- Failure to thrive
- Repeated respiratory infection

##### Examination

- Underweight child
- Bounding pulse
- Wide pulse pressure
- Machinery murmur
- Hepatomegaly

##### Investigation

- ECG: Right ventricular hypertrophy
- Chest X-ray: Cardiac enlargement and pulmonary vasculature

The head circumference was 34 cm. He started taking the breast milk regularly. He had transient tachypnea for 24 hours and it was settled without any intervention. Child was sent home on 5th day of the delivery. Child was afebrile.

## EXAMINATION

On examination, the baby was moderately built and poorly nourished. There was no dysmorphic features. Anthropometric measurements include the length was 64 cm (50th centile), weight was 5 kg (3rd centile), head circumference was 39 cm. The child was afebrile, the pulse rate was 126 per minute bounding and the respiratory rate was 26 per minute. The blood pressure recorded was 60/30 mm Hg. There was no cyanosis.

Cardiovascular examination revealed the presence of marked precordial impulse. The pulmonary component of the second heart sound was loud. A machinery murmur of irregular intensity and low pitch was heard. This was present both in the systole and diastole. It was audible under the left clavicle. The per-abdomen examination shows the enlarged liver size of 5 cm below the costal margin. Respiratory system revealed occasional crepitation at both bases.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 7,400 cells/cu mm
ESR	: 26 mm in the 1st hour
ECG	: Left ventricular hypertrophy (LVH)
X-ray chest	: Cardiac enlargement, pulmonary vasculitis and prominent pulmonary vasculature

## DISCUSSION

A child came with the history of not gaining the weight and with repeated respiratory tract infection. On examination, the presence of the machinery murmur on auscultation, with the bounding pulse, and wide pulse pressure suggests the diagnosis of patent ductus arteriosus (PDA).

The ductus arteriosus is closed postnatally by constriction of smooth muscle in its wall. In full-term infants, this functional closure normally occurs within 10–15 hours after birth; however, complete anatomic obliteration of the ductus arteriosus is slower and may be complete until the third postnatal month. Because pulmonary vascular resistance falls as soon as the lungs expand, in the first 10–15 hours when the ductus arteriosus is still open, a left-to-right shunt through the ductus arteriosus may occur, and a murmur may be heard.

Patent ductus arteriosus is the communication between the left pulmonary artery and descending aorta, i.e., 5 mm distal to the origin of left subclavian artery. PDA occurs in 5–10% of all congenital heart defects (CHDs). It is more common in female, M:F::1:3. It is present in the fetal life. It closes functionally and anatomically soon after birth (1–5 days). The persistence of the ductus arteriosus is called PDA. Sometimes it may be associated with coarctation aorta.

### Causes of Persistent Patency

A clinically apparent PDA occurs in premature infants with birth weights under 1750 g and about 80% with birth weights under 1000 g. The mechanisms responsible for continued patency are due to inability of the ductus arteriosus in immature infants to respond normally to an increased oxygen tension and to changes in prostaglandin concentrations.

When the term infant is found to have PDA there is deficiency of both mucoid endothelial layer and muscular media of the ductus. Premature infants with patent ductus, however has a normal structural anatomy. Patency is the result of immaturity. Hence, PDA closes spontaneously in premature children.

The incidence of persistent patency of the ductus arteriosus in full-term infants born at high altitude is significantly higher than in those born at sea level, probably because of the lower atmospheric oxygen tension. Persistent patency of the ductus arteriosus in full-term and occasional preterm infants at lower altitudes is generally related to a structural abnormality of the ductus arteriosus. Maternal rubella in the first trimester of pregnancy however, is associated with a high incidence of persistent patency of the ductus arteriosus, and rubella virus has been cultured from ductal tissue.

It results in the left to right shunt, i.e., from aorta to pulmonary artery. The flow occurs both during systole and diastole. This is because as pressure

gradient is present throughout the cardiac cycle. The flow of the blood results in murmur. This starts in systole after the first sound. It reaches the peak at second sound. The murmur then diminishes in intensity and it is heard only in a part of diastole. This is the continuous murmur.

Patent ductus arteriosus results in the overloading of the pulmonary artery. The increased flow passing through the lungs reaches the left atrium. Left atrium enlarges to accommodate the flow. It reaches the left ventricle during diastole across the normal mitral valve.

The increased flow at the mitral valve produces the accentuation of the first heart sound and delayed diastolic murmur. The large volume of the blood in the left ventricle causes the prolongation of the left ventricular systole. There will be increase in the size of the left ventricle to accommodate the extra volume. This produces the delayed closure of the aortic valve with large left to right shunt.  $S_2$  may be paradoxically split. The large left ventricular volume is ejected into the aorta. This results in dilatation of the ascending aorta. The dilated ascending aorta results in aortic ejection click.

### CLINICAL FEATURES (FIG. 1)

Patients are usually asymptomatic when the ductus is small. A large shunt PDA is accompanied by tachypnea, hyperdynamic circulation and poor weight gain.

The increased volume load enlarges the left atrium and ventricle, with radiographic evidence of dilation and electrocardiographic evidence of hypertrophy. Because the ascending aorta receives the increased left ventricular output, it is dilated. On chest radiograph, the pulmonary vascular markings indicate increased pulmonary flow.

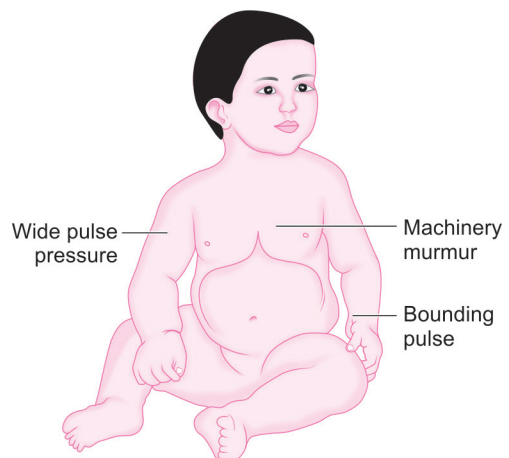


Fig. 1: Clinical features.

If there is pulmonary hypertension, there may be signs of right ventricular pressure overload.

These children become symptomatic in early life. They develop congestive cardiac failure around 6–10 weeks of age. Older children give the history of effort intolerance, palpitations and frequent respiratory tract infections.

On examination, there is prominent bounding carotid pulsation in the neck. A leak from the systemic flow results in the flow from the aortic to pulmonary artery. This produces wide pulse pressure due to diastolic runoff through the ductus. The cardiac impulse is hyperkinetic. The systolic or continuous thrill may be palpated in the second left interspace. The first sound is accentuated. The second sound is loud, narrowly or paradoxically split with large left to right shunting hypertension. Paradoxical splitting is caused by volume overload of the LV and prolonged ejection of blood from this chamber.

The diagnosis of PDA is easier in full-term infants or older children than in premature infants. Because of continuous runoff of blood from the aorta to the pulmonary artery through the ductus arteriosus, the murmur in older infants and children is continuous and has a rumbling, machinery-like or “train in a tunnel” quality usually with late systolic accentuation of the murmur. It is heard best below the left clavicle. If the ductus arteriosus is small, this may be the only abnormal finding.

There is continuous murmur which starts after the first heart sound and it reaches the peak at second sound. The murmur then diminishes in intensity and is audible only during the part of the diastole. The peak at the second sound differentiates the PDA from other cases of the continuous murmur. It is heard at the second left interspace and also as well as below the left clavicle. The other flow murmurs can be mitral delayed diastolic murmur and aortic ejection systolic murmur.

If the shunt is large, recurrent chest infection and congestive cardiac failure (CCF), develop. Reversal of shunt takes place if a large PDA remains untreated and pulmonary hypertension develops. Infective endocarditis is more frequent with small PDA than large one.

#### ESSENTIAL DIAGNOSTIC POINTS

- Variable murmur with active precordium
- Bounding pulses
- More common in newborn premature infants
- Continuous machinery murmur

**ECG:** The ECG shows normal axis with left ventricular dominance or hypertrophy. Deep ‘Q’ waves in the left chest leads with tall ‘T’ waves are characteristic of the volume overload in the left heart. In patients with pulmonary hypertension caused by increased blood flow, biventricular hypertrophy usually occurs.

**Chest radiograph:** The chest radiograph shows the cardiac enlargement. The cardiac size depends upon the size of the left to right shunt. The cardiac size is bigger with larger shunt. There may be left arterial enlargement. The ascending aorta and aortic knuckles are prominent. There is plethoric pulmonary vasculature.

**Echocardiography:** It can be imaged by 2D ECHO in parasternal or suprasternal notch view. The dimension of LA and LV provide an indirect assessment of magnitude of left to right shunt. It confirms the direction and degree of shunting. If suprasystemic pulmonary vascular resistance is present, flow across the ductus will be from right to left.

**Cardiac catheterization:** PDA closure by catheterization with a vascular plug or coils is now routine in but the smallest of neonates.

#### LABORATORY SALIENT FINDINGS

- ECG shows normal axis with left ventricular dominance or hypertrophy. Deep ‘Q’ waves in the left chest leads with tall ‘T’ waves
- **Chest radiograph:** Cardiac enlargement, left arterial enlargement ascending aorta and aortic knuckles are prominent. Plethoric pulmonary vasculature is present
- **ECHO:** Dimension of LA and LV provide an indirect assessment of magnitude of left to right shunt

The evaluation of the size of the left to right shunt depends on a number of features:

- Larger the heart size, larger the left to right shunt
- The wider the pulse pressure, the larger the shunt
- Audible delayed diastolic murmur suggests the large left to right shunt

#### GENERAL FEATURES

- Failure to gain weight
- Congestive cardiac failure
- Repeated respiratory tract infection
- Left ventricular hypertrophy

#### COMPLICATIONS

- Congestive cardiac failure
- Pulmonary arterial hypertension

## DIFFERENTIAL DIAGNOSIS

- Coronary AV fistula
- Ruptured sinus of valsalva
- Aortopulmonary septal defect
- Systemic AV fistula
- Pulmonary AV fistula
- Venous hum

## TREATMENT

In the full-term infant with a PDA, spontaneous closure may occur, but much less commonly than in the premature infant. Medical management, if needed, should be instituted, and at a convenient time, surgical closure should be done.

Even if there is no heart failure, there are two reasons to close a PDA. If there is marked pulmonary hypertension as a result of a large communication, the danger of the development of pulmonary vascular disease necessitates closure, preferably before 6–8 months of age. In the older child with a small PDA, closure is often advised in view of the risk of infective endocarditis, even though this risk is very low. Transcatheter closure with a coil is satisfactory if the diameter of the ductus is below 3 mm, but larger ductus can often be closed by devices such as the Amplatzer duct occluder.

Some ductus still need surgery, either because they are too large for a catheter—introduced device or, conversely, because an extremely premature infant has blood vessels that are too small to accept the large catheter needed to introduce coils or other devices. Surgery can be done safely by open thoracotomy or by thoracoscopy and may be a much shorter procedure than interventional catheterization. The surgical extrapleural approach to ligating the PDA has been shown to be cost effective in developing countries.

Symptomatic PDA is common in preterm infants. Indomethacin a prostaglandin synthesis inhibitor is often used to close PDA in premature infants. Indomethacin does not close the PDA of full-term infants or children. The dose indomethacin is 0.2 mg/kg/dose orally every 12–24 hours for three doses (second and third doses are 0.1 mg/kg/dose for less than 48 hours old and 0.25 mg/kg/dose for less than 7 days old newborn) can be used if there is adequate renal hematologic and hepatic function.

If indomethacin is not effective and ductus remains hemodynamically significant, surgical

ligation should be performed. If ductus partially closes so that if shunt is no longer hemodynamically significant, a second course of indomethacin may be tried.

These patients may develop congestive cardiac failure, if the medical management cannot control the failure, then the patient may need echocardiography or cardiac catheterization for the confirmation of the diagnosis. The aortic valve around the aortic attachment of the PDA becomes more friable in adult life and increases the risk of tear during operation.

Surgical closure is indicated when the PDA and the patient is small. Patients with large left to right shunt require repair by 1 year to the development of progressive pulmonary vascular obstructive disease. Symptomatic PDA with normal pulmonary arterial pressure can safely coil device occluded by catheterization, ideally after child has reached 5 kg.

Surgical indication is the anatomical existence of the lesion. Surgical procedure is performed any time between 6 months and 2 years and anytime in the older child. Procedure involves the ligation and division through left posterolateral thoracotomy, without cardiopulmonary bypass. This is safe procedure. Death occurs in less than 1% of patients.

Patent ductus arteriosus with pulmonary arterial hypertension need cardiac catheterization to exclude aortopulmonary defect. The patients are considered as inoperable if the right to left shunt has appeared because of pulmonary arterial hypertension.

Differential cyanosis occurs if the blood from the right to left shunt through the PDA flows down the descending aorta. Cyanosis is present in toes and not in fingers.

Infective endocarditis prophylaxis is indicated in the presence of small PDA. Catheter closure of ductus with different devices are present. These include double umbrella device, buttoned device and Gianturco coils.

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# Pericarditis with Effusion

## PRESENTING COMPLAINTS

An 8-year-old boy was brought with the complaints of:

- Distension of the abdomen for 6 months
- Tiredness for 2 months

## History of Presenting Complaints

An 8-year-old boy was brought with the history of abdominal distension since last 6 months. His mother gave the history that his son is very weak and gets easily fatigued. She also told that the abdominal distension gradually increased in size. It was uniformly distended. There was no respiratory distress as a result of distension of the abdomen. Mother even told that his son never used to play when other kids play. He used to sit at one place and watches the others playing.

### CASE AT A GLANCE

#### Basic Findings

Height	: 125 cm (70th centile)
Weight	: 25 kg (75th centile)
Temperature	: 37°C
Pulse rate	: 100 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Abdominal distension
- Fatiguability

##### Examination

- Pale
- Increase in jugular venous pressure (JVP)
- Pedal pitting edema
- Muffled heart sounds
- Hepatosplenomegaly
- Shifting dullness

##### Investigation

- Hypoproteinemia (4.8 g/dL)
- Hypoalbuminemia (2.4 g/dL)
- *X-ray chest*: Increase in the size of cardiac silhouette
- *ECG*: Diffuse ST and T wave abnormalities low voltage QRS complex

## Past History of the Patient

He was the only sibling of the nonconsanguineous marriage. He was born at term with normal delivery. There was no significant postnatal event. The baby was discharged on 4th day. The baby was on exclusive breast milk for 6 months. Later weaning was started. He never had any problem. His developmental milestones were normal. His performance at school was good. Occasionally he was complaining of left-sided chest pain. Recently it had increased in frequency.

## EXAMINATION

On examination, the boy was moderately built and moderately nourished. His anthropometric measurements included the height was 125 cm (70th centile), and the weight was 25 kg (75th centile).

He was afebrile. The pulse rate was 100 per minute and respiratory rate was 26 per minute. Blood pressure recorded was 70/50 mm Hg. Jugular venous pressure was raised especially in inspiration. There was no pallor, no lymphadenopathy and no clubbing. Pedal pitting edema was present. Per abdomen examination revealed the presence of abdominal distension. The hepatomegaly was present about 3 cm below the costal margin. It was soft, nontender. Splenomegaly was also present. It was palpable about 2 cm below the costal margin. It was firm and nontender. Shifting dullness was present.

Cardiovascular system revealed, the heart sounds are muffled and no murmur was heard. Respiratory system revealed the presence of coarse crepitations at the base.

## INVESTIGATION

Hemoglobin	: 10 g/dL
Total leukocyte count (TLC)	: 14,000 cells/cu mm
Differential leukocyte count (DLC)	: $P_{72} L_{22} E_4 M_2$
Platelet count	: 3,00,000/cu mm



Total protein	: 4.8 g/dL
Albumin	: 2.4 g/dL
X-ray chest	: Increase in the size of cardiac silhouette and increase in cardio-pericardial shadowing
Electrocardiography (ECG)	: Diffuse ST and T wave abnormalities low voltage QRS complex
Echocardiography (ECHO)	: Pericardium is closely adherent to epicardium. ECHO free space is present in between epicardium and pericardium

## DISCUSSION

Child had fluid overload, manifested by ascites, edema and pulmonary edema. The liver is enlarged because of congestion and not of intraluminal infiltration and left ventricular failure. Raised jugular venous pressure during inspiration is Kussmaul's sign.

The pericardium serves as the external protective layer of the heart providing a barrier to trauma, malignancy, inflammation, and infection. In addition, a thin layer of fluid within the pericardial space lubricates the heart, thereby reducing the energy expenditure and shear stress encountered with cardiac motion. A basic understanding of the anatomy and physiology of the pericardium and pericardial space is necessary to recognize and properly diagnose disease processes affecting this important structure.

The pericardium is a fibrous lining surrounding the heart, consisting of two layers: the parietal (outer) layer and visceral (inner) layer; the visceral layer comes into direct contact with the epicardial surface whereas the parietal layer contains collagenous fibers and serves as an outer protective layer. The pericardium completely envelops the atria and ventricles and terminates just superior to the semilunar valves, it also extends to surround the vena cavae and pulmonary veins near their respective entrances into the heart. Pericardial fluid is a serous, low-viscosity fluid found between the visceral pericardium and the epicardial surface of the heart. In children, approximately 10 mL of fluid is normally found within the pericardial space with larger volumes (20–30 mL) encountered in adults.

Chronic restriction to the right-side venous filling results in hepatic congestion, ascites and pedal edema. Restriction at the left side produces pulmonary venous congestion. This manifests

clinically as basal crepitation, increased frequency of chest infection. Bilateral restriction produces acute onset in cardiac tamponade. Chronic onset is seen in constrictive pericarditis.

The causes of the acute pericarditis include bacterial, viral, tuberculosis, collagen or uremic. The causes of chronic pericarditis tuberculosis, postpyogenic and post-traumatic.

Pericarditis, or inflammation of the pericardium, is the most common cause of pericardial effusion in children. Pericarditis has numerous etiologies, with the most common including viral pathogens. Certain viral infections, such as enteroviruses (coxsackievirus), adenovirus, influenza, and parvovirus, have been associated. It is presumed that most cases of idiopathic pericarditis are related to viral infection, regardless of whether a prodromal illness or evidence of viral infection on laboratory testing is present. Bacterial (purulent) pericarditis is much less common and is associated with *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Neisseria meningitidis* organisms or mycobacterial infection (*Mycobacterium tuberculosis*). Frequently, there is a history of prior or concurrent bacterial infection by the same agent at another site such as osteomyelitis, meningitis, or pneumonia. Unlike viral pericarditis, bacterial pericarditis does not resolve spontaneously and requires intravenous antibiotic therapy with pericardial drainage. The course may be fulminant, and prolonged courses of antibiotics and pericardial drainage are usually required.

Pericardial involvement occurs as a result of infective or inflammatory process. Within 48–72 hours, most cases of pericarditis will develop into the pericardial effusion. There will be accumulation of fluid within the pericardial sac. Clinical picture is determined by the degree of fluid accumulation. The normal amount of the fluid is 15–50 mL. Accumulated fluid may be serous, fibrinous, purulent and hemorrhagic. Cardiac tamponade occurs when the amount of the pericardial fluid reaches the level that compromises cardiac functions.

Pyogenic infection will produce pyopericardium. Even a small amount may be significant clinically. There will be high fever, toxemia and other clinical evidence of pyogenic infection such as pneumonia, empyema and pyoderma. Tuberculosis follows the next. This is followed by viral infection.

The common causes of cardiac tamponade are tuberculosis trauma, uremia, neoplasm and idiopathic.



In some cases, pericardial disease occurs in association with a generalized process. Associations include rheumatic fever, rheumatoid arthritis, uremia, systemic lupus erythematosus, malignancy, and tuberculosis. Pericarditis after cardiac surgery (postpericardiotomy syndrome) is most commonly seen after surgical closure of an atrial septal defect (ASD).

Acute cardiac tamponade is acute heart failure due to the compression of heart by massive rapidly accumulating pericardial effusion in an otherwise nondistensible pericardial sac. There is significant rise in the intrathoracic pressure. There is rise in ventricular and diastolic atrial, systemic and pulmonary venous pressure due to the impaired ventricular relaxation and filling results is poor cardiac output.

## Pericardial Effusion

Pericardial effusion is defined as the excess accumulation of fluid within the pericardial space. It is frequently but not universally, a manifestation of pericardial inflammation. The most common cause of pericardial effusion in children is pericarditis, which in turn has a variety of etiologies.

The causes often pericardial effusion and pericarditis can broadly be categorized into infectious, inflammatory autoimmune, traumatic, toxic, and idiopathic. Infectious etiologies are the most common, most often in conjunction with viral infections associated with pericardial inflammation or as part of a broader cardiac inflammatory process (i.e., myocarditis).

Bacterial seeding of the pericardial space occurs less frequently, however, tuberculosis is a common cause of pericarditis and pericardial effusion in developing countries. Many autoimmune processes may have an associated pericarditis, such as systemic lupus erythematosus, in which pericardial effusion may be a presenting sign of the disease.

Trauma is a common cause of pericardial effusion, via contusion of the heart or direct perforation of the pericardium by penetrating thoracic injury. Several environmental toxins and drugs can be associated with pericardial effusion; in pediatric practice, this is often associated with chemotherapeutic agents or chest irradiation in the setting of treatment for malignancy. Finally, interruption or obstruction of the lymphatic drainage in the chest, usually encountered in the postoperative setting after cardiac surgery in children, may manifest as pericardial effusion with high triglyceride content (chylopericardium).

The hemodynamic effects of pericardial effusion, as well as the presence and nature of symptoms, depend on a number of factors. The size of the fluid collection is the most important determinant of symptoms. In addition, the rate at which a pericardial effusion accumulates has an effect on symptoms. Relatively small accumulations of fluid that develop rapidly (e.g., hemopericardium occurring in the setting of trauma) may be life-threatening; in contrast, in other etiologies with more indolent clinical course, gradual accumulation of pericardial fluid allows time for the pericardium to stretch and therefore adapt to the anatomic and physiologic changes brought about by the presence of sizeable fluid collections.

Pericardial effusions exert their adverse hemodynamic effects by impeding cardiac filling in diastole, which in turn lowers stroke volume and cardiac output. With the accumulation of sufficient pericardial fluid, intrapericardial pressure exceeds atrial pressure leading to collapse of the atrial cavity, impairment of cardiac filling, and limitation of cardiac output, a scenario known as cardiac tamponade. If unrecognized or left untreated, tamponade may quickly progress to circulatory collapse and death.

The initial physiologic response to pericardial effusion is an increase in heart rate, allowing for preservation of cardiac output in the setting of lower stroke volume. Hypotension is a late and ominous finding and may herald impending shock and circulatory collapse. In addition to tachycardia, other physical examination findings in patients with significant pericardial effusions include narrow pulse pressure, jugular venous pulsations, and tachypnea. Hepatomegaly may be present in large effusions that have enlarged gradually. Cardiac auscultation will reveal muffled or distant heart tones. A pericardial friction rub, resembling the crackling sound create by rubbing a tuft of hair between two fingers, will often be present in small pericardial effusions but absent in large collections.

### ESSENTIAL DIAGNOSTIC POINTS

- Retrosternal pain aggravated deep inspiration and relieved leaning forward
- Fever
- Pericardial friction rub
- Tachycardia
- Shortness of breath
- Distention of jugular veins
- Hepatomegaly
- ECG with ST segment

## CLINICAL FEATURES (FIG. 1)

The most common symptom of pericarditis is chest pain, which is usually sharp in nature and localized to the left mid-sternal region. Older patients may describe a sensation of heaviness in the chest, often relieved by leaning forward and exacerbated by inspiration: frequently, there is associated fever. In younger patients, a history of irritability and feeding intolerance is common. Auscultation may reveal a pericardial friction rub, the hallmark physical examination finding in pericarditis.

The chest pain of the pericarditis is dull, sharp and stabbing in nature. The pain radiates to epigastrium, neck, shoulder or left arm. The pain increases on lying down and on deep inspiration, decreasing on sitting down and with forward bending. Child becomes dyspneic and will have cough. The type of fever depends on the etiology.

The pericardial sac is devoid of nerve supply. Hence, the pain is due to adjacent diaphragmatic or pleural irritation. The symptoms and signs in the pericardial effusion are due to the severe cardiac compression, impairment of ventricular diastolic filling, increased systemic pulmonary venous pressure, and eventually due to severely compromised cardiac output and shock.

An important physical examination finding frequently used to assess this risk is known as pulsus paradoxus. Normally, systolic blood pressure varies by a few mm Hg throughout the respiratory cycle, with the blood pressure decreasing during inspiration due to increased intrathoracic pressure. In a hemodynamically significant pericardial effusion, this normal respiratory variation

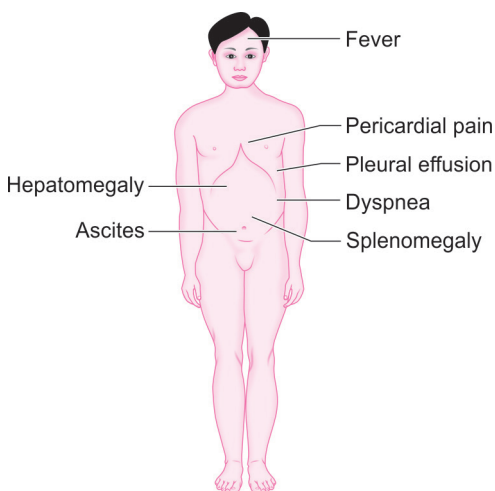
in blood pressure is exaggerated, with systolic blood pressure decreasing by more than 10 mm Hg during inspiration. Pulsus paradoxus is caused by limitation of left ventricular filling in the setting of a significant pericardial fluid collection. Pulsus paradoxus is demonstrated using a manual blood pressure cuff; the patient should be supine and breathing spontaneously.

The blood pressure cuff is inflated, and with deflation, auscultation is used to detect and measure the systolic blood pressure at which the Korotkoff sound is first heard. The cuff is then deflated further; the systolic blood pressure is then detected and measured when the Korotkoff sound is heard continuously during inspiration and expiration. The difference between these two systolic blood pressures is the magnitude of the pulsus paradoxus. The presence of pulsus paradoxus can also be interred through palpation of the pulses (in which an exaggerated change in the amplitude of the pulses can be detected with normal respiration) or in patients with invasive arterial catheters (in which the magnitude of the blood pressure change can be observed on the cardiorespiratory monitor).

The diagnostic physical sign is pericardial friction rub. This is rough scratchy sound. There are three components a systolic, a diastolic and presystolic scratch. This scratchy sound can be heard anywhere over the precardium. Pericardial friction rub is best heard with diaphragm. It is firmly pressed on the sternal border and over the base of the heart. It has to and fro component. It is always in phase with heart sounds.

Physical findings depend on the presence of fluid accumulation in the pericardial space (effusion). If the effusion is large, heart sounds are distant and muffled and a friction rub may not be present. In the absence of cardiac tamponade, the peripheral, venous, and arterial pulses are normal.

In a patient with suspected pericardial effusion, rapid clinical assessment is necessary to determine whether there is evidence of existing or impending cardiac tamponade. If the effusion develops, the cardiac silhouette increases in size. The heart sounds are muffled. These are evidences if peripheral congestion such as raised JVP, hepatomegaly and edema. If the fluid is accumulated rapidly, then the features of cardiac tamponade such as raising jugular venous pressure, paradoxical inspiratory filling of the neck veins, increasing heart rate and pulsus paradoxus appear.



**Fig. 1:** Clinical features.

## GENERAL FEATURES

- Muffled heard sound
- Low voltage QRS complex
- Water bottle configuration

## DIAGNOSIS

Diagnostic testing for suspected pericarditis usually involves an electrocardiogram (ECG), echocardiogram, and laboratory assessment.

Serum inflammatory markers, such as the erythrocyte sedimentation rate and C-reactive protein, are usually elevated, albeit in nonspecific fashion. Serum troponin is a sensitive marker for cardiac injury. In pericarditis, serum troponin is normal or on minimally elevated, this is in contrast to myocarditis, myocardial trauma, or myocardial ischemia.

An echocardiogram is indicated to assess for pericardial effusion, atrioventricular valve regurgitation, and determination of ventricular systolic function. In pericarditis, a pericardial effusion is usually present, and importantly, ventricular function is preserved. The presence of impaired ventricular function, significant atrioventricular or semilunar valvar regurgitation, and/or cardiac chamber dilation is suggestive of an alternative diagnosis, such as myocarditis or cardiomyopathy.

**Ultrasonography:** The diagnosis is easily made with ultrasonography. Areas of collection whether posterior or anterior can be made. In acute cardiac tamponade, ultrasonography shows significant pericardial effusion right atrial collapse, right ventricular diastolic collapse. There will be absent increased early diastolic filling and mitral flow velocity.

**Electrocardiography:** It may show sinus tachycardia with low QRS voltage amplitudes; in severe cases, electrical alternans, the presence of variation in QRS amplitude from beat to beat, can be observed. If there is associated pericarditis or myocarditis, there may be ST-segment and T-wave abnormalities: these changes are more diffusely distributed through the precordial and limb leads compared to the ST-segment and T-wave changes observed with myocardial ischemia.

**Radiograph of chest:** Radiograph of chest shows enlarged cardiac silhouette with water bottle configuration. It shows normal sized heart with ragged or shaggy borders, prominent superior venal shadow margin with right atrial margin. The lung shows pleural effusion.

**ECHO:** Normally echo shows the pericardium is closely adherent to the epicardium. The two layers can only be separated by ultrasound beam.

In patients with effusion, the clear echo free space is present in between epicardium and pericardium. Serial echocardiography allows a direct, noninvasive estimate of the volume of pericardial fluid and its change over time. Cardiac tamponade is associated with compression of the atria or respiratory alteration of ventricular inflow demonstrated by Doppler imaging

## LABORATORY SALIENT FINDINGS

- **ECG:** Diminished QRS voltages and generalized ST segment elevation T wave flattening and inversion.
- Ultrasonography areas of collection whether posterior or anterior can be made.
- Radiograph of chest shows enlarged cardiac silhouette with water bottle configuration, normal sized heart with ragged or shaggy borders, lung show pleural effusion.
- **ECHO:** The ECHO free space between epicardium and pericardium.

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes myocarditis, purulent pericarditis, acute rheumatic fever, juvenile rheumatoid arthritis, uremia and neoplastic disease.

## TREATMENT

Treatment depends on the cause of pericarditis and the size of the associated effusion. Viral pericarditis is usually self-limited and symptoms can be improved with nonsteroidal anti-inflammatory therapy. Purulent pericarditis requires immediate evacuation of the fluid and appropriate antibiotic therapy.

Idiopathic or viral-associated pericarditis is most often a self-limited process, with therapy mainly being supportive. This is in contrast to bacterial pericarditis, in which patients are systemically and often bacteremic. The long-term prognosis for viral-associated pericarditis is favorable, although recurrence may occur in as much as approximately 30% of patients.

Nonsteroidal anti-inflammatory agents (ibuprofen, naproxen and indomethacin) are often useful at alleviating symptoms corticosteroids (prednisone, methylprednisolone) have been used in refractory cases. There has been increasing study of the microtubule assembly inhibitor colchicine in the primary treatment of pericarditis, which in recent studies has been demonstrated to be superior to nonsteroidal anti-inflammatory drugs alone in effecting the resolution of symptoms. Colchicine also has value in the prevention of recurrent pericarditis. There is limited experience with the use of colchicine in infants and very young children.

Cardiac tamponade from any cause must be treated by immediate removal of the fluid, usually via pericardiocentesis. Pericardiocentesis should also be considered if the underlying cause is unclear or identification of the pathogen is necessary for targeted therapy. In the setting of recurrent or persistent effusions, a surgical pericardiectomy or pericardial window may be necessary. Diuretics should be avoided in the patient with cardiac tamponade because they reduce ventricular preload and can exacerbate the degree of cardiac decompensation.

## Pericardiocentesis

Pericardiocentesis is done for diagnostic purpose, but if the collection is large resulting in tamponade, therapeutic removal of significant amount of fluid becomes essential.

Viral effusion needs only symptomatic treatment. It resolves spontaneously in 2–4 weeks. Other conditions such as collagen vascular disease are treated appropriately and effusion resolves slowly with steroids. Surgical drainage is rarely indicated unless the fluid is thick and fibrinous. Surgical decortication is indicated in constrictive pericarditis.

For patients with symptomatic pericardial effusion, impending cardiac tamponade, or rank tamponade, gentle drainage of the fluid (pericardiocentesis) by percutaneous means may be lifesaving, surgical drainage of pericardial effusion is usually limited to patients with bacterial pericarditis or in patients with chronic, recurrent effusions (pericardial window). In the presence of tamponade, temporizing medical therapy includes oxygen, fluid resuscitation to augment preload, and avoidance of agents that decrease systemic vascular resistance. Diuretics, sometimes used in small effusions without hemodynamic compromise, should be avoided if there is concern for tamponade.

Pericardiocentesis is usually performed with real-time echocardiographic guidance. A long needle is advanced into the pericardial space from the subxiphoid region, with brisk flow of fluid from the needle confirming entry into the pericardial space. Frank blood from the needle may indicate hemopericardium or entry into heart itself. After acute drainage of fluid, a catheter is usually advanced over a wire into the pericardial space to allow for continued drainage while the inciting process for the effusion resolves, pericardial fluid should be sent for cell count analysis, Gram stain, cytology, and culture for diagnostic purposes, testing of pericardial fluid via polymerase chain

reaction (PCR) methods is available and can rapidly identify many viral etiologies of pericarditis.

In pyogenic pericardial effusion, the pus in the pericardial sac is surgically drained after the institution of appropriate antibiotics. Tuberculosis effusion is treated with a minimum of three anti-tubercular drugs and initial course of steroids. Chronic constrictive pericarditis is treated surgically. It can be prevented by early pericardiectomy.

## Postpericardiotomy Syndrome

Postpericardiotomy syndrome is a distinct entity encountered in children after cardiac surgery at which the pericardium has been opened. Postpericardiotomy syndrome typically presents with fever beyond the first postoperative week (without evidence of infection elsewhere), new pericardial effusion, chest pain, friction rub, and in some cases, new pleural effusions. It is encountered in all age groups and surgeries, but for unclear reasons, it appears to be more commonly encountered in patients who have undergone atrial surgery (e.g., surgical atrial septal defect repair, atrioventricular canal defect repair). It is also common after heart transplantation. The etiology is uncertain but is felt to have an inflammatory component. Patients may present several weeks to months after surgery, so it is important for clinicians to be aware of this diagnosis in patients with a history of cardiac surgery. Treatment includes nonsteroidal anti-inflammatory agents and pericardiocentesis for large fluid collections.

## PROGNOSIS

Prognosis depends to a great extent on the cause of pericardial disease. Constrictive pericarditis can develop following infectious pericarditis (especially if bacterial or tuberculous) and can be a difficult problem to manage. Cardiac tamponade will result in death unless the fluid is evacuated.

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# Sydenham's Chorea

## PRESENTING COMPLAINTS

A 9-year-old girl was brought with the complaints of:

- Abnormal movement since 2 months
- Difficulty in holding the pen since 1 month

## History of Presenting Complaints

A 9-year-old girl with a history of involuntary movements came to the pediatric outpatient department. The mother told that her daughter developed the involuntary movements 2 months back. In the beginning the movements were minimal which increased later on. The movements were observed to be aggravated by stress and emotional instability. The movements used to be irregular, nonrepetitive involving mainly distal parts, i.e., fingers and toes. The girl used to have difficulty in holding pen or spoon. These involuntary movements used to be absent in the night.

### CASE AT A GLANCE

#### Basic Findings

Height	: 128 cm (50th centile)
Weight	: 26 kg (75th centile)
Temperature	: 37°C
Pulse rate	: 96 per minute
Respiratory rate	: 18 per minute
Blood pressure	: 90/60 mm Hg

#### Positive Findings

##### History

- Girl
- Involuntary movements
- Past history of joint pain

##### Examination

- Clumsy look
- Distal involuntary movements
- Pallor
- Sustained contraction at knee joint

##### Investigation

- ESR: 32 mm
- ASLO: 400 Todd units

## Past History of the Patient

She was the second sibling of the nonconsanguineous marriage. She was born at full term after normal delivery. There was no significant postnatal event. The child's developmental milestones were normal.

Her performance at school was satisfactory. There was a past history of joint pain, fever and throat pain. For these complaints she had been treated by the general practitioner.

## EXAMINATION

On examination, the girl appeared more clumsy with a reserved look to control her involuntary movements. She was moderately built and nourished. The anthropometric measurements included her height was 128 cm (50th centile), the weight was 26 kg (75th centile). She was afebrile, her heart rate was 96 per minute and respiratory rate was 18 per minute. The blood pressure recorded was 90/60 mm Hg.

There was pallor, no lymphadenopathy, no icterus and no clubbing. Throat was clear. Involuntary movements were mainly found in the distal part of the extremities. The movements were nonrepetitive and quasi-purpose. Tongue used to be out of the mouth. Knee jerk showed some sustained contraction. All the systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 9 g/dL
TLC	: 8,800 cells/cu mm
ESR	: 32 mm in 1st hour
ASLO	: 400 Todd units
CRP	: 1250 µg/dL (Normal range: 67–1800 µg/L)
X-ray chest	: Normal
ECG	: Normal

## DISCUSSION

Chorea may precede or follow other manifestations of the rheumatic fever. It usually occurs in the later



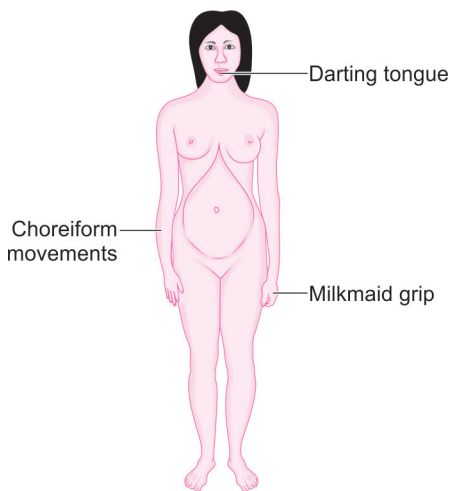
part of the rheumatic fever. It is one of the major criteria of the diagnosis of the rheumatic fever. One-third of these patients develop rheumatic valvular heart disease. The usual age of onset of the disease is 5–15 years.

It is an autoimmune response to central nervous system (CNS) to Group A streptococcal organism. Antineural antibodies cross react with cytoplasm of the subthalamic and caudate nuclei. The primary pathological changes include vasculitis of the cortical arterioles, round cell infiltration of the gray and white matter.

### CLINICAL FEATURES (FIG. 1)

Chorea is the functional overactivity of the dopaminergic system. Classically, the movements are described as irregular, nonrepetitive, quasi-purpose and involuntary. They are usually proximal but may affect fingers, hands, extremities and face. The child may appear clumsy. Movements may be limited to one side of the body as in hemiballismus. The movements are aggravated by attention, stress or excitement. But they disappear during sleep.

The relaxing hand grip, on and off as if she is milking the cow-milkmaid sign. The child cannot maintain the tongue in protruded position-darting tongue. The knee reflex may show sustained contractions resulting in a hung-up reflex. Anti-streptolysin O titer (ASLO titer) may not be elevated as onset of the chorea is late.



**Fig. 1:** Clinical features.

### GENERAL FEATURES

- Movements aggravated by stress, attention
- Absent at the time of sleep

### ESSENTIAL DIAGNOSTIC POINTS

- Acute onset of choreiform movement
- Associated with rheumatic endocarditis and arthritis
- Autoimmune response to CNS to Group A streptococcal organism
- Classically, the movements are described as irregular, nonrepetitive, quasi-purpose and involuntary

### DIFFERENTIAL DIAGNOSIS

- Huntington's chorea
- Wilson's disease
- Hyperthyroidism
- Systemic lupus erythematosus (SLE)

### LABORATORY SALIENT FINDINGS

- Anemia
- Leukocytosis
- Increased ESR
- ASLO CRP may be raised
- ECG Echo to find cardiac problems
- Antineural antibodies are present
- EEG shows nonspecific seizure activity
- MRI SPECT may show basal ganglia abnormalities

### TREATMENT

This disorder is usually self-limiting and may last for few weeks to few months. Child should be protected from the injury. These children may be treated with chlorpromazine, haloperidol, sodium valproate, or carbamazepine.

The dosage is determined by minimum doses for the symptom suppression. Aspirin and steroid help to limit the course of the chorea and are the important modalities of treatment in resistant cases. Antistreptococcal prophylaxis with penicillin G should be given to prevent recurrence of the rheumatic activity.

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# Tetralogy of Fallot

## PRESENTING COMPLAINTS

A 3-year-old boy was brought with the complaints of:

- Breathlessness for 1 day
- Bluish color of the lips for 2 hours
- Floppy for 1 hour

## History of Presenting Complaints

A 3-year-old boy was brought to the pediatric casualty with the history of bluish color of the lips and breathlessness. The mother of the boy told that the child was normal before going to bed last night. In the morning he first developed difficulty in breathing and became breathless. Later he developed the bluish color of the lips and became floppy. Then the child was brought to the hospital where he was treated with oxygen.

### CASE AT A GLANCE

#### Basic Findings

Height	: 100 cm (90th centile)
Weight	: 12 kg (80th centile)
Temperature	: 37°C
Pulse rate	: 116 per minute
Respiratory rate	: 36 per minute
Blood pressure	: 90/60 mm Hg

#### Positive Findings

##### History

- Bluish color
- Floppy
- Known tetralogy of Fallot (TOF)

##### Examination

- Cyanotic spell
- Polycythemia
- Clubbing
- Ejection systolic murmur

##### Investigation

- Hemoglobin: 18 g/dL
- X-ray chest: Boot-shaped heart
- ECG: Right axis deviation
- ECHO: Hypertrophied right ventricle

## Past History of the Patient

The boy was born at full-term with normal delivery. He cried immediately after the delivery. He was stable at birth. There was no bluish color at the time of delivery. There was no significant postnatal event except for transient tachypnea, which was settled within 24 hours.

Child was on breast milk for 6 months and weaning started later with cereals and fruits. He was on family food by the age of 15 months. Mother gave history of the dusky coloration of the lips at the age of 3 months while crying. Then he had been completely evaluated and diagnosed to have Fallot's tetralogy. Later at the age of 15 months, he became bluish even at rest. Mother had noticed the child becomes floppy at the time of bluish color.

## EXAMINATION

The child appears moderately built and nourished. He was having breathlessness and uncomfortable. He was floppy. Anthropometric measurements included his height was 100 cm (above 90th centile), the weight was 12 kg (above 80th centile).

He was febrile. The pulse rate was 116 per minute and the respiratory rate was 36 per minute. The blood pressure recorded was 90/60 mm Hg. There was no pallor. Clubbing was present. Cyanosis was evident.

Cardiovascular system revealed the presence of single pulmonary second sound. Ejection systolic murmur was heard over the left second intercostal space. Other systemic examination was normal.

## INVESTIGATION

Hemoglobin	: 18 g/dL
TLC	: 12,000 cells/cu mm
DLC	: $P_{74} L_{20} E_2 M_2$
ESR	: 26 mm in the 1st hour
ECG	: Right axis deviation

ABG	: pH—7 PaCO <sub>2</sub> —55 mm Hg PaO <sub>2</sub> —45 mm Hg HCO <sub>3</sub> —18 mEq/L
X-ray chest	: Boot-shaped heart with prominent right ventricle— pulmonary oligemia and hyperlucent lung field
ECHO	: Hypertrophied right ventricle with a small outlet. Overriding of aorta on the ventricle and VSD

## DISCUSSION

A 3-year-old boy presented with cyanosis and breathlessness, and it was relieved after medical management. On examination, child was cyanosed and clubbing was present. Cardiovascular system revealed ejection systolic murmur. This along with chest radiograph, electrocardiograph (ECG) and ECHO findings, the diagnosis of Fallot's tetralogy was made. Tetralogy of Fallot (TOF) occurs in 10% of all congenital heart diseases (CHDs). This is the most common cyanotic CHD, seen beyond infancy.

It is the most common cyanotic congenital heart disease in a child above the age of 2 years. Anatomically, it consists of ventricular septal defects (VSDs) associated with obstruction at right ventricular outflow. This is in the form of infundibular or infundibular plus valvular pulmonic stenosis. The RV hypertrophies, not because of pulmonary stenosis, but because it is pumping against systemic resistance across a (usually) large VSD. Atrial septal defect (ASD) occurs in 15%.

Obstruction to RV outflow with a large VSD causes a right-to-left shunt at the ventricular level with arterial desaturation. The greater the obstruction and the lower the systemic vascular resistance, the greater is the right-to-left shunt. TOF is associated with deletions in the long arm of chromosome 22 (22q11, DiGeorge syndrome) in as many as 15% of affected children. This is especially common in those with an associated right aortic arch.

The basic lesion is anterocephaloid malalignment of the outlet septum relative to the muscular septum. This is associated with unequal division of the truncus arteriosus into small pulmonary and large aortic components. The malalignment together with secondary hypertrophy of the muscle form the primary site of obstruction to blood flow in the infundibulum or outflow tract of the right ventricle. In addition, the pulmonary valve is often

stenotic, and the pulmonary valve annulus and pulmonary arteries are often hypoplastic.

The four constituents of tetralogy include: ventricular septal defect, pulmonic stenosis, overriding or dextroposed aorta and right ventricular hypertrophy. Other associated features are right aortic arch in 25% of cases. Pulmonic annulus and main pulmonary artery are hypoplastic. Abnormal coronary artery is present.

In the most severe form of TOF with pulmonary atresia, the distal infundibular outflow tract and pulmonary valve are atretic. The pulmonary artery and main pulmonary arterial branches may be severely hypoplastic or atretic. Often, large aortopulmonary collaterals supply most of the lung. The ventricular septal defect is usually large, perimembranous with outlet extension, and near the tricuspid and aortic valves. The aorta arises directly over the ventricular septal defect; the degree of overriding varies greatly.

Pulmonic stenosis causes concentric right ventricular hypertrophy without cardiac enlargement and an increase in right ventricular pressure. When the right ventricular pressure is as high as left ventricular or the aortic pressure, the right to left shunt appears to decompress the right ventricle. Increasing severity of the pulmonary stenosis reduces flow of blood into the pulmonary artery, and increases right to left shunt. Because of the pulmonary outflow tract obstruction, varying amounts of systemic venous blood are shunted across the ventricular septal defect into the aorta, resulting in cyanosis. Pulmonary artery pressure and pulmonary blood flow are reduced.

The flow from the right ventricle into the pulmonary artery occurs across the pulmonic stenosis produces an ejection systolic murmur. The more severe the pulmonic stenosis shorter will be the ejection systolic murmur, and more the cyanosis. Thus, the severity of the cyanosis is directly proportional to the severity of the pulmonic stenosis. The intensity of the systolic murmur is inversely related to severity of pulmonic stenosis.

Since right ventricle is effectively decompressed by ventricular septal defects, congestive cardiac failure never occurs. But it can occur if there are anemia, infective endocarditis, systemic hypertension, myocarditis and aortic or pulmonary wall regurgitation.

The right ventricular outflow obstructions produce delay in P2. The ascending aorta is large and may result in aortic ejection click. Concentric right ventricular hypertrophy reduces the distensibility of the right ventricle during diastole.

The right atrial contraction at the end of diastole causes a relatively large 'a' waves. In acyanotic TOF, i.e., VSD with mild PS, long pansystolic murmur resulting from VSD and infundibular stenosis is audible. Ejection systolic murmur is heard in pulmonary area. Cyanosis is absent.

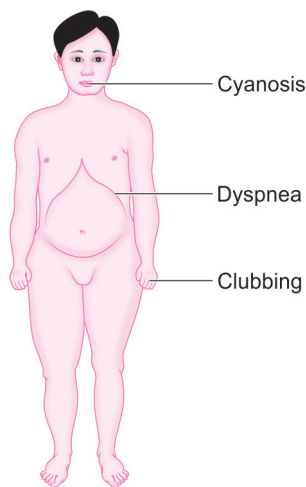
### CLINICAL FEATURES (FIG. 1)

The clinical findings at birth vary with the severity of the pulmonary stenosis, but few infants with the TOF remain asymptomatic or acyanotic. Cyanosis may not be present at birth; as long as the ductus arteriosus remains patent, there may be adequate pulmonary blood flow, or the outflow tract obstruction may not be severe at birth.

The patient may become symptomatic any time after birth. Neonates may develop anoxic spell. The most common symptoms are dyspnea on exertion, and exercise intolerance. The patients assume a squatting posture as soon as they become dyspneic.

Most cases of TOF are mildly cyanosed at birth. Exertional dyspnea, squatting, hypoxic spells develop later in life. Acyanotic TOF with a large VSD will present with congestive cardiac failure. Presence of severe cyanosis at birth signifies atresia with VSD.

Clinical findings vary with the degree of RV outflow obstruction. Patients with mild obstruction are minimally cyanotic or acyanotic. Those with severe obstruction are deeply cyanotic from birth. Few children are asymptomatic those with significant RV outflow obstruction, many have cyanosis at birth, and nearly all have cyanosis by age 4 months. The cyanosis usually is progressive, as subvalvular obstruction increases.



**Fig. 1:** Clinical features.

Physical examination shows a right ventricular systolic heave along the lower left sternal border. A single loud second heart sound corresponding to aortic valve closure is generally heard best at the lower left sternal border, rather than being heard best at the upper right or both the upper right and left sternal border. This physical sign is important, especially in a neonate when trying to differentiate an acyanotic TOF from a ventricular septal defect. When closure of the pulmonary valve is audible at the upper left sternal border, it is delayed and diminished in intensity.

In patients with moderate right ventricular outflow tract obstruction, the mid-to-high pitch systolic murmur is loud and harsh, stenotic or pansystolic in quality, and best heard at the middle or lower left sternal border. Rarely, a continuous murmur of persistent ductus arteriosus is heard at the upper left sternal border. As there is less ejection through an increasingly stenotic pulmonary outflow tract, the murmur will shorten in duration and will increase in pitch.

Growth and development are not typically delayed, but easy fatigability and dyspnea on exertion are common. The fingers and toes show variable clubbing depending on age and severity of cyanosis. Infants who are acyanotic at birth, become cyanosed by 8–12 weeks of life. Hypoxic spell may develop depending upon the right ventricular obstruction. Brain abscess, cerebrovascular accidents and infective endocarditis are occasional complications. Since central cyanosis predisposes to polycythemia, iron deficiency anemia and coagulopathy are common.

Hypercyanotic episodes with paroxysmal hyperpnea may occur spontaneously or after early morning feedings or prolonged crying the attacks may last only a few moments and have no sequelae, they may cause obtundation, limpness, deep exhaustion, or sleep; rarely, they may end in unconsciousness, convulsions, or even death.

Hypoxemic spells, also-called cyanotic or "Tet spells," are one of the hallmarks of severe TOF. 'These spells can occur spontaneously and at any time, but in infants occur most commonly with crying or feeding, while in older children they can occur with exercise. They are characterized by (1) sudden onset of cyanosis or deepening of cyanosis; (2) dyspnea; (3) alterations in consciousness, from irritability to syncope; and (4) decrease or disappearance of the systolic murmur (as RV the outflow tract becomes completely obstructed). These episodes most commonly start as age 4–6 months.

Because approximately one-third of patients with the TOF begin to have hypoxic spells by 4 or 5 months of age, palliative or corrective surgery is usually done electively within a young children with the TOF and severe cyanosis often adopt a characteristic squatting position after exertion. This maneuver increases arterial oxygen saturation, probably by increasing systemic arterial resistance. A final group of patients shows little or no evidence of cyanosis in infancy or early childhood (acyanotic TOF); cyanosis on exertion gradually becomes more manifest as they grow older.

In TOF, the dilated aortic root overrides a large adjacent ventricular septal defect, and varying degrees of right ventricular infundibular obstruction, pulmonary valve stenosis, and hypoplasia or narrowing of the main pulmonary artery and left pulmonary artery are revealed by echocardiogram. Doppler examination confirms the severity of the obstruction and demonstrates systolic turbulence in the main pulmonary artery.

The acute severe episodes of dyspnea and hypoxemia, termed blue spells or hypercyanotic episodes, in some infants with the TOF reflect a further acute reduction in the pulmonary blood flow. These spells may occur even if the infant is not cyanotic at rest. The precipitating mechanisms are probably multiple: prolonged crying may decrease pulmonary blood flow because of prolonged expirations; decreases in right ventricular preload and systemic vascular resistance because of sleeping, fever, or spontaneous vasomotor changes decrease pulmonary blood flow and increase the right-to-left shunt and constriction of the right ventricular infundibulum may occur further decreasing pulmonary blood flow, although it is uncertain whether this truly occurs.

Cyanotic spells are treated acutely by administration of oxygen and placing the patient in the knee-chest position (to increase systemic vascular resistance). Intravenous morphine should be administered cautiously, but is helpful for its sedative effect. Propranolol produces beta-blockade and may reduce the obstruction across the RV outflow tract through its negative inotropic action. Acidosis, if present, should be corrected with intravenous sodium bicarbonate. Chronic oral prophylaxis of cyanotic spells with propranolol may be useful to delay surgery, but the onset of Tel spells usually prompts surgical intervention. In fact, in the current era, elective surgical repair generally occurs around the age of 3 months so as to avoid the development of Tet spells.

On examination, there is cyanosis, clubbing, and prominent 'a' waves in JVP. There will be mild parasternal heave and systolic thrill is present. Ejection systolic murmur is present. Aortic ejection click may be heard. There is tachycardia.  $S_2$  is usually single in pulmonary area because aortic component is heard to dextroposed and overriding of aorta. The only indirect evidence of VSD is the presence of cyanosis. The acyanotic TOF, VSD with mild PS—long pansystolic murmur resulting in VSD and infundibular stenosis is audible. Ejection systolic murmur is heard in pulmonary area. Cyanosis is absent.

In the rare, untreated patient, major late complications include brain abscess, cerebral thrombosis with hemiplegia, and infective endocarditis. Growth and development are generally delayed in proportion to the degree of cyanosis. Infective endocarditis is particularly common in children who have palliative systemic-pulmonary shunts rather than correction. Prophylactic antibiotic therapy is no longer routinely recommended for most of these repaired patients, although unrepaired or palliated patients still require prophylaxis.

#### GENERAL FEATURES

- Anoxic spell
- Convulsions
- Loss of consciousness

#### ESSENTIAL DIAGNOSTIC POINTS

- Cyanosis after neonatal period
- Hypoxemic spells during infancy
- Systolic ejection murmur at upper left sterna border
- Right sided aortic arch

### DIAGNOSIS

Hemoglobin, hematocrit, and red blood cell count are usually elevated in older infants or children secondary to chronic arterial desaturation.

*The radiograph of chest:* It shows normal sized heart with upturned apex suggestive of right ventricular hypertrophy. The absence of main pulmonary artery segment gives it the shape as coeur-en-sabot. The pulmonary fields are oligemic.

The heart is of normal size, and lung fields are poorly vascularized, signifying diminished pulmonary blood flow. The right ventricular outflow tract and main pulmonary artery segments are usually hypoplastic, resulting in a concavity of the upper left margin of the cardiac silhouette instead of the normal convexity. The RV is hypertrophied, often shown by an upturning of

the apex (boot-shaped heart). A characteristic “sheep’s nose, coeur en sabot, or boot-shaped heart may be present, particularly with pulmonary atresia. The ascending aorta is generally large. In about 25% of the patients, a right-sided aortic arch is present and is recognized by observing a right-sided rather than left-sided indentation on the trachea. The superior vena caval shadow may be displaced to the right. When bronchial collateral circulation is well developed, diffuse fine vascular markings are noted throughout the lung.

**ECG:** Right axis deviation (+120 – +150), with right ventricular hypertrophy in cyanotic form. In acyanotic QRS axis is normal. Electrocardiograph shows large overriding of the aorta, right ventricular hypertrophy and outflow obstruction. Aortic mitral valve continuity is maintained. “T” waves are inverted in right precordial leads. “P” pulmonale may be present. There are right-axis deviation and right ventricular hypertrophy, although in the newborn infant, the diagnosis of pathologic right ventricular hypertrophy by electrocardiogram is more difficult because of the normal right ventricular dominance at this age.

**Echocardiography:** Two-dimensional ECHO and Doppler studies can make diagnosis and assess the severity of TOF. A large perimembranous infundibular VSD and overriding of aorta are visualized in long axis parasternal view. Right ventricular outflow tract obstruction with pulmonary valve and annulus are present. Doppler studies estimate the pressure gradient across right ventricular outflow tract.

Two-dimensional imaging is diagnostic, revealing thickening of the RV wall, overriding of the aorta, and a large subaortic VSD. Obstruction at the level of the infundibulum and pulmonary valve can be identified, and the size of the proximal pulmonary arteries measured. The anatomy of the coronary arteries should be visualized, as abnormal branches crossing the RV outflow tract are at risk for transection during surgical enlargement of the area.

**Cardiac catheterization and angiocardiography:** Pressure gradients may be noted at the pulmonary valvular level, the infundibular level, or both. RV angiography reveals RV outflow obstruction and a right-to-left shunt at the ventricular level. The major indications for cardiac catheterization are to establish coronary artery and distal pulmonary artery anatomy if not able to be clearly-defined by echocardiography.

#### LABORATORY SALIENT FINDINGS

- The radiograph of chest shows normal sized heart with upturned apex suggestive of right ventricular hypertrophy. The absence of main pulmonary artery segment gives it the shape as coeur-en-sabot. The pulmonary fields are oligemic.
- Electrocardiograph (ECG) shows large overriding of the aorta, right ventricular hypertrophy and outflow obstruction.
- **ECHO:** A large perimembranous infundibular VSD and overriding of aorta are visualized in long axis parasternal view. Right ventricular outflow tract obstruction with pulmonary valve and annulus.
- Doppler studies estimate the pressure gradient across right ventricular outflow tract.

#### COMPLICATIONS

- Anemia
- Infective endocarditis
- Anoxic spell
- Hemiplegia
- Paradoxical embolism
- Brain abscess
- Right bundle branch block (RBBB)

#### TREATMENT

As with many significant congenital heart abnormalities, the treatment is ultimately surgical. For the neonate with prominent cyanosis, prompt infusion of PGE<sub>1</sub> is important. Corrective or palliative surgery is usually performed within 2–4 months of birth, but in the rare patient who has not had surgery, medical therapy is primarily directed toward acute relief of hypercyanotic episodes and preventing the complications of right-to-left shunts.

Hypercyanotic episodes may be treated by placing the infant on the abdomen in a knee-chest position or holding the infant with the legs flexed on the abdomen. Oxygen should be given to lessen dyspnea and cyanosis but is not very helpful because of the very low pulmonary blood flow. Morphine sulfate (0.2 mg/kg body weight subcutaneously) is especially effective in terminating a prolonged or severe attack. If the spell is protracted and severe and does not respond to the foregoing therapy, metabolic acidemia ensues, and intravenous fluid bolus administration and correction with intravenous sodium bicarbonate are essential.

Vasopressors can be given either early in the attack or if other therapy fails; phenylephrine, 0.02 mg/kg intravenously or 0.1 mg/kg intramuscularly, will raise systemic resistance and



thus increase pulmonary blood flow. If possible, phenylephrine should be given by continuous intravenous infusion, generally at a dose of 2–5 hg/kg/min. Recently a nasal fentanyl spray of 2 hg/kg was reported as being effective. In infancy, these attacks may be precipitated by a relative iron-deficiency anemia (hypochromic microcytic), and such patients should have iron therapy until the hematocrit reaches levels of 50–55%.

Further increase in the hematocrit results in a marked rise in blood viscosity, with progressive impediment to blood flow a risk of cerebral thrombosis. Any hypercyanotic episode is an absolute indication for surgery, so it is now rare to need to treat anemia except in the immediate preoperative period. If surgery is contraindicated for some reason, oral propranolol has been given at a dosage of 0.5–1.5 mg/kg dose orally every 6 hours to prevent or reduce the frequency of paroxysmal dyspneic attacks. Some cardiologists have reported that balloon dilation and stent placement of the infundibulum and pulmonary valve may improve pulmonary blood flow enough for 6–12 months in the case that surgery needs to be delayed or is unavailable.

Medical management is limited to the management of complications, and correction of anemia. The management of the anoxic spell includes:

- Knee chest position
- Humidified oxygen
- Morphine 0.1–0.2 mg/kg subcutaneous injection
- Sodium bicarbonate is given to correct the acidosis
- Propranolol in the dose of 0.1 mg/kg during the anoxic spell
- Vasodilators
- Correction of anemia
- Surgery

The surgical treatment is of two types, palliative and definitive.

Indications for palliative shunt procedure:

- Neonate with TOF and pulmonary atresia
- Infants with hypoplastic pulmonary annulus and hypoplastic pulmonary artery stenosis.
- Severely cyanotic infants. Younger than 3 months and those who have medically unmanageable hypoxic spells.

Palliative treatment consists of anastomosing a systemic artery with the pulmonary artery. This increases the pulmonary blood flow and thus increases the oxygenated blood flow reaching the systemic circulation.

Early elective surgery is indicated for infants with TOF with or without pulmonary atresia, even in the absence of symptoms. Patients with the TOF and patent right ventricular outflow tracts can have intracardiac surgical repair of the malformation by skilled congenital heart surgeons in the 1st month of life with low operative mortality. The ventricular septal defect is closed, the infundibular muscle is resected, and sometimes right ventricular outflow and main pulmonary artery patches are placed to augment the outflow tract. Pulmonary valvotomy is also performed in most patients, but enlargement of the pulmonary valve annulus with a transannular patch is avoided unless the annulus is critically small.

Balloon dilation of the pulmonary arteries can then be performed in the catheterization laboratory in anticipation of later correction.

Although repair of TOF with pulmonary atresia has in recent years become increasingly successful, the operative risk and late complications and death are higher than for uncomplicated TOF. Unifocalization of the often-discontinuous sources of pulmonary blood flow to a central system is required before the standard repair. This may be done in one or multiple stages.

Surgical correction for most patients with uncomplicated TOF results in excellent survival. Residual or recurrent small left-to-right shunts are uncommon, but residual mild or moderate right ventricular-pulmonary outflow tract obstruction and regurgitation are common those who have marked pulmonary regurgitation and very dilated right ventricles may eventually develop congestive heart failure and may be at higher risk for sudden death, especially if they have very wide QRS intervals. These patients are candidates for pulmonary valve replacement, currently primarily performed surgically but increasingly being performed by catheter insertion. A few patients have surgically induced complete AV block and require an implanted pacemaker. Dysrhythmias should be suspected if these patients after surgery complain of dizzy spells, syncope, or palpitations, and appropriate diagnostic studies and therapy applied.

Balloon dilatation of RV outflow tract and pulmonary valve has been attempted to delay surgical repair.

*Blalock-Taussig shunt* : Subclavian artery and pulmonary artery

*Pott's shunt* : Descending aorta to pulmonary artery

*Waterston's shunt* : Ascending aorta and right pulmonary artery



Most preferred method is Blalock-Taussig shunt. Here the basic heart disease remains unaltered.

### **Conventional (Definitive) Repair Surgery**

It is indicated in symptomatic infants who have favorable anatomy of RV outflow tract and pulmonary artery stenosis. An early repair is advised, any time after 4 months of age. Mildly cyanotic children who have had shunt surgery, total repair 1–2 years after shunt operation.

The definitive operation consists of closing the ventricular septal defect and resecting infundibular obstruction.

Open-heart surgery for repair of TOF is performed at ages ranging from birth to 2 years, depending on the patient's anatomy and the experience of the surgical center. The current surgical trend is toward earlier repair for symptomatic infants. The major limiting anatomic feature of total correction is the size of the pulmonary arteries. During surgery the VSD is closed and the obstruction to RV outflow removed. Although a valve sparing procedure is preferred, in many cases a transannular patch is placed across the RV outflow tract as the pulmonary valve is contributing to the obstruction. When a transannular patch repair is done, the patient has pulmonary insufficiency that is usually well tolerated for years. However, pulmonary valve replacement is eventually necessary once symptoms (usually exercise intolerance) and right ventricular dilation occur. Surgical mortality is low.

This is done under cardiopulmonary bypass. The major complications include complete

heart block, right bundle branch block, residual ventricular septal defect and residual pulmonic stenosis. If the pulmonary arteries are adequate in size, and the arteries descending coronary artery is from left coronary artery, a patient with anoxic spell can be subjected to definitive repair even at the age of 3–6 months.

### **COURSE AND PROGNOSIS**

Infants with severe TOF are usually deeply cyanotic at birth. These children require early surgery. Complete repair before age 2 years usually produces a good result, and patients are currently living well into adulthood. Depending on the extent of the repair required, patients frequently require additional surgery 10–15 years after their initial repair for replacement of the pulmonary valve.

Patients with TOF are at risk for sudden death due to ventricular dysrhythmias. A competent pulmonary valve without a dilated RV appears to diminish arrhythmias and enhance exercise performance.

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# Ventricular Septal Defect

## PRESENTING COMPLAINTS

A 4-month-old girl was brought with the complaints of:

- Not gaining weight since 2 months
- Cough and cold since 1 month
- Fever since 1 month
- Sweating since 15 days

## History of Presenting Complaints

A 4-month-old girl with history of not gaining weight was brought to the pediatric outpatient department. The mother told that her child birth weight was 3 kg. When she was taken for immunization at 6 weeks, the weight of the child was 2.75 kg. At the time of second dose of diphtheria-pertussis-tetanus (DPT) and oral polio vaccine (OPV) at 10 weeks, the weight of the child

was 3 kg. When she went to the hospital last week for the cough and cold, the weight of the child was 3.5 kg. The mother also noticed that child sweats at the time of taking feeds. She had been treated by the doctor for the lower respiratory tract infections.

## Past History of the Patient

Girl was the only sibling of the nonconsanguineous marriage. She was born at full-term through vaginal delivery. She cried immediately after the delivery. The birth weight was 3 kg. There was no significant postnatal event. The child was taking breast milk and was discharged on the 4th day.

The resident at the time of birth had auscultated and found the systolic murmur. It was brought to the notice of the consultant. Parents were advised to attend the cardiac clinic for assessment of murmur. According to the mother the child was getting repeated respiratory tract infections and she was receiving the treatment. She developed the respiratory tract infection and was irritable.

### CASE AT A GLANCE

#### Basic Findings

Length	: 60 cm (75th centile)
Weight	: 3.5 kg (<3rd centile)
Temperature	: 38°C
Pulse rate	: 140 per minute
Respiratory rate	: 46 per minute
Blood pressure	: 60/48 mm Hg

#### Positive Findings

##### History

- Failure to thrive
- Sweating
- No gain in weight
- Murmur at birth
- Repeated infections

##### Examination

- Underweight
- Pallor
- Systolic thrill
- Hepatomegaly
- Tachypnea
- Febrile

##### Investigation

- Hb: 9 g/dL
- ECG: Biventricular hypertrophy
- X-ray chest: Enlarged heart with pulmonary plethora, left atrial enlargement

## EXAMINATION

The child was moderately built and poorly nourished. She was irritable and breathless. Sub-costal recession was present. The intercostal and accessory muscles were active. Anthropometric measurements included the length was 60 cm (75 centile) and weight was 3.5 kg (less than 3rd centile). The head circumference was 39 cm.

She was febrile. The pulse rate was 140 per minute, the respiratory rate was 46 per minute. Blood pressure recorded was 60/48 mm Hg. There was pallor, no lymphadenopathy and no edema.

Sternum was prominent. Apex beat was displaced to the anterior auxiliary line. Systolic thrill was felt to the left lower sternal edge on auscultation, pulmonary component of the second sound was loud. Pansystolic murmur was present over the left 3rd and 4th inter-costal space.

Respiratory system was normal and per abdomen examination revealed the presence of enlarged liver about 3 cm below the costal margin. It was soft and nontender.

## INVESTIGATION

Hemoglobin	: 9 g/dL
TLC	: 9,800 cells/cu mm
DLC	: $P_{68} L_{30} E_2$
ESR	: 36 mm in the 1st hour
AEC	: 346 cells/cu mm
ECG	: Biventricular hypertrophy
X-ray chest	: Enlarged heart with pulmonary plethora, cardiomegaly and left atrial enlargement

## DISCUSSION

A 4-month-old child was brought with the history of inability to gain weight and breathlessness. On examination, there was systolic thrill associated with pansystolic murmur. Radiograph of chest showed the presence of the enlarged heart with pulmonary plethora and electrocardiograph suggested biventricular hypertrophy. All these findings suggest ventricular septal defect (VSD).

A ventricular septal defect usually occurs as an isolated abnormality but may be associated with other congenital cardiac malformations. In view of the pattern flow in the heart and great vessels of a fetus with a ventricular septal defect, with diversion of blood from the aortic isthmus, narrowing the aortic isthmus or true coarctation should always be considered when an infant with a ventricular septal defect has severe heart failure. Ventricular septal defects are also common in corrected transposition of the great arteries. They are always present in a truncus arteriosus communis and in a double-outlet right ventricle (DORV) that, in the absence of pulmonic stenosis, has the clinical features of an isolated ventricular septal defect.

Ventricular septal defect is the most common congenital heart malformation, accounting for about 30% of all congenital heart disease. Defects in the ventricular septum occur both in the membranous portion of the septum (most common) and the muscular portion.

It is the communication between the two ventricles. It can be present in membranous or muscular part of septum. Ninety percent of the ventricular septal defects are present in the membranous part. It can be multiple. It accounts for 20% of all CHDs.

The muscular septum has two components, the inlet (trabecular) septum and the outlet (infundibular) septum. The trabecular septum has three components—central, marginal and apical. A VSD may be classified into perimembranous outlet (infundibular), central muscular, marginal muscular and apical muscular defects. 'Bundle of His' is related to posteroinferior quadrant

of perimembranous defect and superoanterior quadrant of inlet muscular defect.

The large volume of the blood passing through the lungs is seen as pulmonary plethora. The increased volume of the blood finally reaches the left atrium. This leads to left atrial enlargement. Then passing through the normal mitral valve produces delayed diastolic murmur at the apex. It is directly related to the size of the shunt. The large flow across the mitral valve also results with accentuation of the first heart sound.

Left ventricle has two outlets, aortic valve allowing forward flow, ventricular septal defect leads to backward leak. It empties relatively early. This results in early A2 since ejection into the right ventricle and pulmonary artery is increased because of left to right shunt P2 is delayed. Therefore, second sound is widely split but varies with respiration.

VSDs follow one of four courses:

1. *Small, hemodynamically insignificant ventricular septal defects:* Between 80 and 85% of VSDs are small (<3 mm in diameter) at birth and will close spontaneously. In general, small defects in the muscular interventricular septum will close sooner than those in the membranous septum. In most cases, a small VSD never requires surgical closure. Fifty percent of small VSDs will close by age 2 years, and 90% by age 6 years, with most of the remaining closing during the school years.
2. *Moderate-sized ventricular septal defects:* Asymptomatic patients with moderate-sized VSDs (3–5 mm in diameter) account for 3–5% of children with VSDs. In general, these children do not have clear indicators for surgical closure. Historically, in those who had cardiac catheterization, the ratio of pulmonary to systemic blood flow is usually less than 2:1, and serial cardiac catheterizations demonstrate that the shunts get progressively smaller. If the patient is asymptomatic and without evidence of pulmonary hypertension, these defects can be followed serially as some close spontaneously over time.
3. *Large ventricular septal defects with normal pulmonary vascular resistance:* These defects are usually 6–10 mm in diameter. Unless they become markedly smaller within a few months after birth, they often require surgery. The timing of surgery depends on the clinical situation. Many infants with large VSDs and normal pulmonary vascular resistance develop symptoms of failure to thrive, tachypnea, diaphoresis with feeds by age 3–6 months,

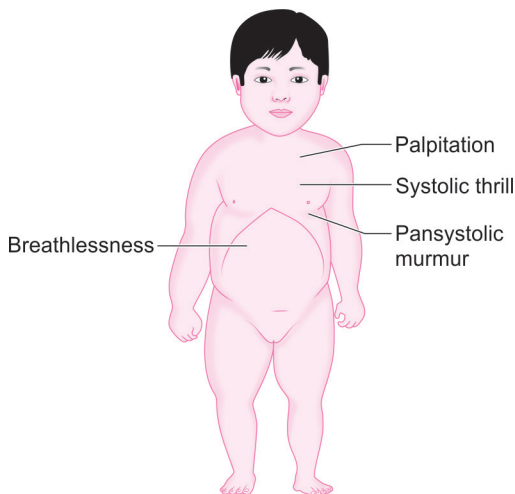
and require correction at that time. Surgery before age 2 years in patients with large VSDs essentially eliminates the risk of pulmonary vascular disease.

4. **Large ventricular septal defects with pulmonary vascular obstructive disease:** The direction of flow across a VSD is determined by the resistance, in the systemic and pulmonary vasculature, explaining why flow is usually left-to-right. In large VSDs, ventricular pressures are equalized, resulting in increased pulmonary artery pressure. In addition, shear stress caused by increased volume, in the pulmonary circuit causes increased resistance over time. The vast majority of patients with inoperable pulmonary hypertension develop the condition progressively. Almost all cases of irreversible pulmonary hypertension can be prevented by surgical repair of a large VSD before age 2 years.

## CLINICAL FEATURES (FIG. 1)

### Symptoms and Signs

Patients with small or moderate left-to-right shunts usually have no cardiovascular symptoms. Patients with large left-to-right shunts are usually ill early in infancy. These infants have frequent respiratory infections and gain weight slowly. Dyspnea, diaphoresis, and fatigue are common. These symptoms can develop as early as 1–6 months of age. Older children may experience exercise intolerance. Over time, in children and adolescents with persistent large left-to-right shunt, the pulmonary vascular bed undergoes structural changes, leading to increased pulmonary vascular resistance and reversal of the shunt from left-to-right to right-to-left



**Fig. 1:** Clinical features.

(Eisenmenger syndrome). Cyanosis will then be present.

- **Small left-to-right shunt:** No lifts, heaves, or thrills are present. The first sound at the apex is normal, and the second sound at the pulmonary area is split physiologically. A grade II-IV/VI, medium- to high-pitched, harsh pansystolic murmur is heard best at the left sternal border in the third and fourth intercostal spaces. The murmur radiates over the entire precordium. No diastolic murmurs are heard.
- **Moderate left-to-right shunt:** Slight prominence of the precordium with moderate LV heave is evident. A systolic thrill may be palpable at the lower left sternal border between the third and fourth intercostal spaces. The second sound at the pulmonary area is most often split but may be single. A grade III-IV/VI, harsh pansystolic murmur is heard best at the lower left sternal border in the fourth intercostal space. A mitral diastolic flow murmur indicates that pulmonary blood flow and subsequently the pulmonary venous return are significantly increased by the large shunt.
- **Large ventricular septal defects with pulmonary hypertension:** The precordium is prominent, and the sternum bulges. Both LV and RV heaves are palpable. S2 is palpable in the pulmonary area. A thrill may be present at the lower left sternal border. S2 is usually single or narrowly split, with accentuation of the pulmonary component. The murmur ranges from grade I to IV/VI and is usually harsh and pansystolic. Occasionally, when the defect is large or ventricular pressures approach equivalency, a murmur is difficult to hear. A diastolic flow murmur may be heard, depending on the size of the shunt

Uncomplicated VSD may present with:

- Pulmonic stenosis due to hypertrophy right ventricular infundibulum
- Pulmonary atrial hypertension
- Aortic regurgitation due to prolapse of right coronary or noncoronary cusp of aortic valve.

## DIAGNOSIS

### Chest X-ray

In patients with small shunts, the chest radiograph may be normal. Patients with large shunts have significant cardiac enlargement involving both the left and right ventricles and the left atrium. The main pulmonary artery segment may be dilated. The pulmonary vascular markings are increased.

## Electrocardiography

The ECG is normal in small left-to-right shunts. Left ventricular hypertrophy (LVH) usually occurs in patients with large left-to-right shunts and normal pulmonary vascular resistance. Combined ventricular enlargement occurs in patients with pulmonary hypertension caused by increased flow, increased resistance, or both. Pure RV hypertrophy occurs in patients with pulmonary hypertension secondary to pulmonary vascular obstruction induced by long-standing left-to-right shunt (Eisenmenger syndrome).

## Echocardiography

Two-dimensional echocardiography can reveal the size of a VSD and identify its anatomic location. Multiple defects can be detected by combining two-dimensional and color-flow imaging. Doppler can further evaluate the VSD by estimating the pressure difference between the left and right ventricles. A pressure difference greater than 50 mm Hg in the left ventricle compared to the right ventricle confirms the absence of severe pulmonary hypertension.

## Cardiac Catheterization and Angiocardiology

The ability to describe the VSD anatomy and estimate the pulmonary artery pressures on the basis of the gradient across the VSD allows for the vast majority of isolated defects to be repaired without cardiac catheterization and angiocardiology. Catheterization is indicated in those patients with increased pulmonary vascular resistance. Angiocardigraphic examination defines the number, size, and location of the defects.

## TREATMENT

Isolated ventricular septal defects are the most common types of congenital heart disease, so all pediatricians need to know how they can be managed.

Spontaneous closure may eventually occur in up to 70% of patients, and many of these closures occur by 3 years of age. In a further 25%, the defect becomes smaller but may not close completely; however, the hemodynamic effects are significantly reduced. Because of these statistics, if the defect seems to be becoming smaller, surgical correction should be delayed in the hope of spontaneous closure.

Primary surgical closure of the defects can be done with very low mortality. If primary closure is

not feasible because of multiple muscular defects or other complicating factors, then banding the pulmonary artery will decrease the left-to-right shunt, reduce the pulmonary flow and pressure, and relieve congestive heart failure. Banding has its own complications, and removal of the band when the defect is closed later adds to the morbidity of the procedure.

Muscular defects, especially if multiple, can be difficult to close surgically. From a right ventriculotomy, the masses of hypertrophied trabeculae are daunting and make the defect(s) difficult to find. Although a left ventriculotomy simplifies surgery, a large incision in the systemic ventricle should be avoided. Some surgeons cut away all the right ventricular trabeculae to make closing the defect easier, and others suture all the trabeculae together to close the exit holes. Because of the difficult surgery, closing the muscular defect by catheter introduction of an Amplatzer device is being used more often. Some catheterization procedures are very lengthy, and an alternative is to use a hybrid method in which a surgeon performs a small thoracotomy and the Amplatzer device is inserted more directly through a trocar. Some cardiologists have even used similar devices for nonsurgical closure of perimembranous ventricular septal defects, but this procedure has more risk of producing complete AV block and of damaging the aortic valve.

## Medical Management

It consists control CCF, chest infections and prevention and treatment of anemia and infective endocarditis. Patients who develop symptoms can be managed with anticongestive treatment, particularly diuretics and systemic afterload reduction, prior to surgery or if it is expected that the defect will close over time.

## Surgical Treatment

### *Surgical Indications*

- Large VSDs with nonresponding CCF should be closed in the first 6 months of life.
- Significant L-R shunt with QP/QS of at least 2:1 indicates surgical closure.
- Older infants with large VSDs and increased pulmonary resistance.

In large VSDs, infundibular stenosis may develop which decreases the magnitude of L-R shunt (acyanotic TOF).

Patients with cardiomegaly, poor growth, poor exercise tolerance, or other clinical abnormalities who have a significant shunt (>2:1) typically



undergo surgical repair at age 3–6 months. The operative treatment consists of closure of the VSD with the use of Dacron patch. It can be performed through the right atrium. The operation can be done below the age of 1 year if the congestive cardiac failure cannot be controlled with medical management. With the evidence of pulmonary hypertension, it can be done by the age of 2 years. As a result, Eisenmenger syndrome has been virtually eliminated. The surgical mortality rate for VSD closure is below 2%.

Transcatheter closure of muscular VSDs is also a possibility. Perimembranous VSDs have also been closed in children during catheterization, but a high incidence of complete heart block after placement of the occluding device has slowed the acceptance of this approach.

The complications of the surgery include complete heart block, bifascicular block and residual ventricular defect. Postoperative follow-up includes SBE prophylaxis and pacemaker implantation in the presence of heart blocks. Surgical mortality 2–5% after the age of 6 months. It is higher in smaller infants less than 2 months or with associated defects.

## COMPLICATIONS

In some infants with significant reductions in left-to-right shunts caused by spontaneous closing of the ventricular septal defects, mid to late systolic clicks have become audible. In these children, aneurysmal dilation of the thin membranous septum or tricuspid valve tissue that has grown to close the defect has occurred, with bulging of pseudoaneurysm into the right ventricle. A small opening often present at the apex of the pseudoaneurysm allows a small left-to-right shunt. Normally, the defect closes, and the pseudoaneurysm slowly shrink but rarely it may enlarge progressively. These pseudoaneurysms be demonstrated by echocardiography.

A number of infants have developed progressive aortic insufficiency associated with ventricular septal defect, particularly if it is subarterial. There is prolapse of an aortic valve leaflet with dilation of the aortic valve sinus, and distortion or even rupture of the aortic sinus or cusp may occur. The development of aortic insufficiency has been attributed to stress on the unsupported aortic cusp and perhaps suction on it by the jet of the shunt passing through the defect. Even with a small ventricular septal defect, or one showing the evidence of closure, aortic insufficiency requires surgical closure of the

defect to prevent further prolapse. It may in fact be prudent to close subarterial ventricular septal defects even before evidence of aortic valve cusp involvement is apparent.

Infective endocarditis can occur even after spontaneous closure of the defect. If infective endocarditis involves the tricuspid leaflet sealing the ventricular septal defect, rupture may occur and produce a direct left-ventricular-to-right-atrial communication. Previously, antibiotic prophylaxis for infective endocarditis had been recommended for children with even small defects.

## COURSE AND PROGNOSIS

Significant late dysrhythmias are uncommon. Functional exercise capacity and oxygen consumption are usually normal, and physical restrictions are unnecessary. Adults with corrected defects have normal quality of life.

### GENERAL FEATURES

- Congestive cardiac failure
- Failure to thrive
- Frequent chest infection

### ESSENTIAL DIAGNOSTIC POINTS

- Cyanotic
- Easy fatigability
- Congestive cardiac failure in infancy
- Hyperactive heart
- Biventricular enlargement
- Grade 2.3/4 pansystolic murmur maximum at lower sterna border
- P2 is usually accentuated
- Diastolic flow murmur at apex.

### LABORATORY SALIENT FINDINGS

- ECG shows combined ventricular hypertrophy. Right ventricular hypertrophy is seen with Eisenmenger's complex.
- *Chest radiograph*: Pulmonary vasculature is increased. Left atrial enlargement with the large left to right shunt.
- Echocardiogram shows increased left atrial and ventricular size and exaggerated mitral valve motion.

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# Acute Gastroenteritis

## PRESENTING COMPLAINTS

A 3-year-old girl was brought with the complaints of:

- Loose motion since 2 days
- Vomiting since 1 day
- Fever since 1 day

## History of Presenting Complaints

A 3-year-old girl was brought to pediatric outpatient department with history of loose motion and vomiting since 2 days. According to the mother, her daughter was passing loose motion about 7–8 times per day. When child had the loose motion it was semisolid and later it became watery, not associated with blood and mucus. Mother also told that her child had vomiting on the first day. Child was vomiting whatever she was taking. Vomitus used to contain the ingested food material. Mother also revealed that she had noticed fever since morning.

### CASE AT A GLANCE

#### Basic Findings

Height	: 100 cm (90th centile)
Weight	: 13 kg (80th centile)
Temperature	: 38°C
Pulse rate	: 120 per minute
Respiratory rate	: 32 per minute
Blood pressure	: Not recordable

#### Positive Findings

##### History

- Vomiting
- Loose motion
- Drowsy
- Fever

##### Examination

- Febrile
- Signs of moderate to severe dehydration
- Sunken eyes
- Blood pressure not recordable
- Loss of skin elasticity
- Bowel sounds: Vigorous

##### Investigation

- Stool examination: 8–10 pus cells

## Past History of the Patient

She was the only child of nonconsanguineous marriage. She was born at full-term by normal vaginal delivery. There was no significant post-natal event. The baby was on breast milk soon after the delivery. Weaning was started in the fourth month and completed by one year. All the developmental milestones were normal. She was completely immunized.

## EXAMINATION

The girl was moderately built and nourished. She was in altered sensorium, i.e., drowsy because of dehydration. Signs of moderate to severe dehydration were present. Eyes were sunken, child was tired, loss of skin elasticity was present.

Anthropometric measurements included, the height 100 cm (90th centile), the weight 13 kg (80th centile) and the child was febrile. Pulse rate was 120 per minute and respiratory rate was 32 per minute and blood pressure was not recordable.

There was no pallor, no lymphadenopathy, no cyanosis and no clubbing. Per abdomen examination revealed mild distension, bowel sounds were vigorous. There was no organomegaly. Respiratory and cardiovascular system revealed no abnormalities.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 7600 cells/cu mm
DLC	: P <sub>80</sub> L <sub>18</sub> E <sub>2</sub>
Stool routine	: 8–10 pus cells Reducing substance negative
Electrolytes	: Na 110 mEq/L K: 4 mEq/L Cl: 8 mEq/L
BUN	: 20 mg/dL
Serum creatinine	: 1 mg/dL

## DISCUSSION

Gastroenteritis is caused by an infective agent that damages the gut mucosa and disturbs the balance

between the mechanism controlling secretion and absorption within the bowel. The excessive net loss of electrolytes and water into the gut lumen results in diarrhea characterized by passing of frequent unformed stools in the well-nourished child case. Acute diarrheal disease tends to be self-limiting with minimum mortality. Prolonged diarrhea is more common among malnourished or very young infants and is associated with an increase in mortality and morbidity.

The term diarrhea refers to the passage of three or more loose stools per day. Diarrhea is a symptom and it is preferable to consider diarrhea if there is increased frequency, volume and fluidity. Diarrhea is defined as an increase in the liquidity and/or frequency of the stools and can be a primary feature of both acute and chronic conditions. It reflects an increase in stool water content due to impaired water absorption and/or active water secretion by the intestine. It is also a sign when the loss of water is more than 15 g/kg/day in children less than 3 years of age and more than 200 g/kg/day in children more than 3 years of age.

### Acute Diarrhea

The term acute diarrhea refers to a condition where the child passes loose stools lasting for 3–7 days.

### Intermediate Diarrhea

The term intermediate diarrhea includes children with acute onset of diarrhea lasting for 8–14 days.

### Dysentery

It is the term used for diarrhea with visible blood and mucus, often associated with fever and tenesmus.

Diarrheal disease is an important problem of children less than 5 years of age and in this age group the primary target are children between 6 months and 2 years of age. As the child grows older, the incidence decreases.

Breastfeeding has a definite impact on the occurrence of diarrheal diseases. Infants who are breastfed have a lower incidence of infective diarrhea. The protective factors in breast milk prevent diarrhea. The early introduction of cow's milk and commercial formulae increase the incidence of diarrhea.

The early introduction of weaning foods will not only be a source of infection but also result in macromolecular absorption of allergens and predispose to the onset and perpetuation of

diarrhea. This is more evident if breast milk is discontinued at the time of weaning. Exclusive breastfeeding is therefore recommended till the age of 6 months.

The incidence of diarrhea is more in bottle fed infants than in breastfed infants. When top milk is essential the child should be given teaspoon feeding or “paladai” feeding. This form of feeding is much superior to bottle feeding as the utensils can be cleansed properly.

Diarrhea and malnutrition form a vicious cycle and the nutritional status may worsen after an episode of diarrhea. Malnutrition is also a precipitating factor in predisposing to persistent diarrhea.

The presence of associated infections like urinary tract infections, acute suppurative otitis media, bronchopneumonia and sepsis in a child with acute diarrhea are well recognized precipitating factors for progression to persistent diarrhea if not treated promptly.

There are certain factors which are peculiar to children and infants which can aggravate the effects of diarrhea. They are:

- The greater body content of water in infants
- The larger turnover of water in the infant as compared to adults
- The greater insensible loss of water, since the surface area is 2–3 times that of an adult
- The greater metabolic requirements
- The immaturity of the kidney in handling solutes and the poor concentrating capacity
- The inability of the infant to quench his thirst by drinking water.

### Types of Acute Diarrhea

Acute diarrhea can present as:

- Acute watery diarrhea.
- Acute dysentery

### Etiology

#### ETIOLOGY OF ACUTE WATERY DIARRHEA

##### Infections

- Viruses—Rota, Adeno, Calici, Norwalk, HIV
- Bacteria—*Vibrio cholerae*, *Escherichia coli*, *Salmonella*, *Shigella*, *Staphylococci*, *Aeromonas hydrophila*, *Plesiomonas shigelloides*
- Protozoa—Giardiasis, cryptosporidiasis and *E. histolytica*
- Fungal—*Candida*
- Systemic infections—LRTI, UTI, AOM

*Diet:* Food intolerance, food allergy and food poisoning

*Systemic illness:* Metabolic disorders, renal disease, endocrinopathy

Contd...

Contd...

**Antibiotics**

**Surgical causes:** Appendicitis, intussusception, short bowel syndrome

**Miscellaneous:** Encopresis

### ETIOLOGY OF ACUTE DYSENTERY

**Infective causes**

- *Escherichia coli*—Enterohemorrhagic (EHEC), enteroinvasive (EIEC)
- *Shigella*—*S. dysenteriae*
- *Campylobacter jejuni*
- *Salmonella*
- *Yersinia enterocolitica*
- *Entamoeba histolytica*

**Noninfective causes**

- Pseudomembranous colitis
- Inflammatory bowel disease
- Radiation-induced colitis
- Segmental enteritis

The term 'parenteral diarrhea' refers to a clinical state in many children who present with diarrhea where the primary disease may be outside the gastrointestinal tract, e.g., otitis media, respiratory or urinary tract infection.

**Pathophysiology:** Most episodes of diarrhea occurs secondary to 1 of 5 types of mechanisms: malabsorptive, secretory, osmotic, dysmotility, and inflammatory.

1. **Malabsorption diarrhea:** Malabsorption is due to a decrease in absorptive surface area, as occurs after intestinal resection (short bowel syndrome) or with intestinal villous atrophy, as seen in celiac disease. Secretory diarrhea is caused by secretagogues such as bacterial toxins (e.g., cholera), gut regulatory peptides (e.g., vasoactive intestinal polypeptide), short-chain fatty acids, and bile salts, which can induce intestinal water secretion while inhibiting absorption.
2. **Osmotic diarrhea:** Osmotic diarrhea is a term used when the presence of unabsorbed or poorly absorbed osmotically active solutes (e.g., lactose) creates an osmotic load and inhibits water absorption, leading to a net secretion of water and consequently osmotic diarrhea. Osmotic diarrhea characteristically decreases or stops completely during fasting. The lower electrolyte concentration in osmotic diarrhea suggests that some other osmotic substance is contributing to the isotonic osmotic load in the fluid expelled from the colon.
3. **Secretory diarrhea:** This refers to diarrhea caused by abnormal ion transport in intestinal

epithelial cells. A net secretory state develops in the gastrointestinal tract (GIT) as a result of reduced absorption or increased secretion of ions and water. It can be due to:

- Abnormal mediators—Bacterial endotoxin
- Diffuse mucosal disease
- Intestinal resection
- Congenital defect of ion transport

Secretory diarrhea characteristically persists even when the patient is in a fasting state. Osmotic diarrhea results from the intraluminal presence of malabsorbed solutes, such as lactose, which exert significant osmotic pressure that results in secretion of water into the intestines. Secretory diarrhea does not alter with eating and the osmolality of the stool can be accounted for by normal ionic constituents. Therefore, doubling the sum of sodium and potassium concentrations in stool should equal the fecal osmolality.

4. **Inflammatory diarrhea:** Inflammation due to shigella produces ulcerations in the small intestine and colon which can cause diarrhea. This results in the passage of pus, mucus, serum and blood in addition to water and electrolytes. Inflammatory disorders cause diarrhea by several mechanisms including release of prosecretory eicosanoids and cytokines; altered tight junction function, decreasing the mucosal absorptive capacity or the capacity to reabsorb bile acids; and/or disturbances in motility.
5. **Motility diarrhea:** Increased motility can cause diarrhea by reducing the contact time of chyme with the intestinal epithelium. The reduced motility can also cause diarrhea by allowing small bowel bacterial growth, bile acid deconjugation and malabsorption. In contrast to secretory diarrhea, dysmotility can lead to increased peristalsis, causing diarrhea due to rapid transit, or to decreased peristalsis, causing diarrhea due to bacterial overgrowth. Motility disorders affecting the anorectum and reflexes involved in defecation may cause an increase in stool fluidity and frequency without increase in weight.

Intestinal pathogens causing diarrhea and/or vomiting:

- **Viruses:** Rotavirus, adenovirus, and others
- **Bacteria:** *Escherichia coli*, *Shigella*, *Salmonella*, *Campylobacter jejuni*, *Yersinia enterocolitica*, *Aeromonas*, and others.
- **Parasites:** *Entamoeba histolytica*, *Giardia lamblia*, and *Cryptosporidium*.

## CLINICAL FEATURES (FIG. 1)

**Diarrhea:** it is wise to ask specifically about the number and character of the stools, as the notion of what constitutes 'diarrhea' varies widely. Severity is often underestimated because of initial pooling of secretion in the gut or because watery diarrhea is easily mistaken for urine. Blood in the stools suggests an invasive organism (*Shigella*, amoebae, or necrotizing enterocolitis) or a hemorrhagic colitis induced by enema therapy with toxic substances. Blood-stained stools may also occur in *Campylobacter* infection. Frothy stools suggest carbohydrate intolerance. Pale malodorous stools suggest steatorrhea and infection with *Giardia lamblia*.

**Vomiting:** Usually it is present but its severity is variable may precede diarrhea by hours or even a day, particularly in cases of viral etiology. If bile-stained or persistent, surgical conditions must be excluded.

**Constitutional signs:** Fever and toxicity are uncommon and their presence suggests parenteral or viral etiology. An abrupt onset of diarrhea with high fever and no vomiting is characteristic of *Shigella* enteritis.

**Dehydration:** Dehydration occurs in a minority of cases but is the most common complication of gastroenteritis. If untreated, dehydration accounts for 60–70% of gastroenteritis deaths. Accurate and immediate assessment is critical to management. Measurement of weight changes is the most accurate method of assessment but is usually not available initially, making clinical assessment necessary.

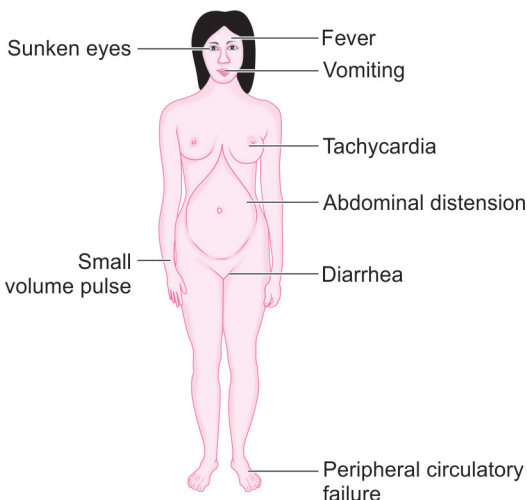


Fig. 1: Clinical features.

**Acidosis:** Invariably present if there are signs of dehydration, characterized by deep, sighing respiration and an anxious appearance. Persistence of acidosis suggests that dehydration has not been corrected.

Metabolic alkalosis virtually excludes the diagnosis of gastroenteritis. The most common cause in protracted vomiting is pyloric stenosis or other surgical conditions.

### GENERAL FEATURES

- Dehydration
- Acidotic breathing
- Seizures
- Generalized edema
- Oliguria
- Thirst
- Dry mucus membrane
- Sunken anterior fontanelle

**Ileus:** A distended, relatively silent abdomen suggests this diagnosis. This acute 'toxic' dilatation of the gut may be caused by infection, toxemia, or hypokalemia. Potassium supplementation reduces the incidence of this complication. Necrotizing enterocolitis can occur in young malnourished infants who have had an episode of shock. It presents with signs of ileus and blood in the stools.

**Seizures:** These are quite common but their cause is often obscure. Causes to be excluded are fever, hypoglycemia, electrolyte disturbances (e.g., sodium, calcium and magnesium), cerebral vein thrombosis and meningitis. Seizures with fever at the onset of illness suggests shigella enteritis. Seizures and the disturbances of central nervous function, such as coma, drowsiness, irritability and hyper-reflexia, are more common in hypernatremic dehydration.

### ESSENTIAL DIAGNOSTIC POINTS

- Diarrhea
- Vomiting
- Dehydration
- Drowsiness
- Irritability
- Seizures
- Ileus
- Acidosis

## DIAGNOSIS

Clinical examination is necessary to exclude parenteral disease and systemic infections such as meningitis. Consider the possibility of surgical conditions, particularly if there is persistent or bile-stained vomiting, gross abdominal distension or redness and edema of the abdominal wall.

Dehydration is the most common complications and must initially be assessed clinically. Regular weighing thereafter allows an objective measure of the process of rehydration. Many complications follow on dehydration.

Assessment of Dehydration (Table 1)

Dehydration is the single most important cause of morbidity and mortality in acute diarrhea, and the assessment of its severity is of utmost importance in the choice of fluid therapy.

Dehydration is classified as mild, moderate or severe. In infants, fluid losses of 5% (50 mL/kg) and 10% (100 mL/kg), roughly correspond to the moderate and sever grades respectively. In older children and adults, fluid loss of 3%, 5% and 7% corresponds to mild, moderate and severe grades respectively. Some authors use 3%, 6% and 9% for the older children.

Additional features (Table 2) such as sunken anterior fontanelle, thready pulse, shallow breathing and decreased urine output, can also be included to grade the severity of dehydration. Treatment Plan A is for those with no dehydration, Plan B for mild and moderate dehydration and Plan C is for severe dehydration.

Diagnosis

If there is no more than mild dehydration, most cases of gastroenteritis can be managed without further investigation. In severe cases, it may be useful to measure the plasma electrolytes, urea and glucose and to determine the acid-base status, but if these results are not immediately available, do not delay the treatment of shock and dehydration.

Diagnosis of acute diarrhea is based on clinical history of passing frequent, loose or watery stools, with or without vomiting, fever, pain in abdomen or blood in the stools. Many children may have symptoms and signs of other associated illnesses

like cough, skin rashes/measles or urinary symptoms. The clinical trial of rotaviral diarrhea is fever, vomiting and profuse watery stools with tendency for dehydration.

Dehydration is the most common and life-threatening consequence of diarrhea. Loss of water and electrolytes in the diarrhea/stool results in depletion of the extracellular fluid (ECF) volume, electrolyte imbalance and clinical manifestation of dehydration. The first symptom of dehydration appears after fluid loss of 5% of body weight. When fluid loss reaches 10%, shock often sets in, and the cascade of events that follows can culminate in death unless there is immediate intervention to rehydrate.

Routine stool examination is not recommended except in situations such as young infants with fever, suspected protozoan *Giardia* and *Entamoeba histolytica* as a cause, extra-gut infections or persistent colitis or disaccharide intolerance and prolonged/persistent diarrhea with malnutrition. Stool culture is invariably noncontributory.

Diarrhea when prolonged or recurrent, is a major cause of malnutrition in children, owing to use of bottle feeds, stoppage of breastfeeds and lack of energy dense feeds and hygiene like hand washing, low food intake during the illness (poor appetite, vomiting, oral thrush or stomatitis, diluting/withholding of food, etc.), reduced nutrient absorption in the intestines, and increased requirements as a result of infection. Repeated and prolonged episodes of diarrhea have even more deleterious effects and may eventually result in growth failure, intercurrent infections and problems associated with severe malnutrition and even death.

Microbiology of stools (microscopy and culture) is necessary if a definite etiological diagnosis is required. The clinical characteristics of the illness may be helpful in identifying the probable infective agent, but in most cases symptoms and signs are

TABLE 1: Features of dehydration.

	Mild	Moderate	Severe
1. Look at: Condition <ul style="list-style-type: none"><li>– Eyes</li><li>– Tears</li><li>– Mouth and tongue</li><li>– Thirst</li></ul>	<ul style="list-style-type: none"><li>• Well, alert</li><li>• Normal</li><li>• Present</li><li>• Moist</li><li>• Drinks normally, not thirsty</li></ul>	<ul style="list-style-type: none"><li>• Restless, irritable</li><li>• Sunken</li><li>• Absent</li><li>• Dry</li><li>• Thirsty, drinks eagerly</li></ul>	<ul style="list-style-type: none"><li>• Lethargic or unconscious; floppy</li><li>• Very sunken and dry</li><li>• Absent</li><li>• Very dry</li><li>• Drinks poorly or not able to drink</li></ul>
2. Feel: Skin pinch	Goes back quickly	Goes back slowly	Goes back very slowly >2 seconds
3. Decide: Hydration status	No signs of dehydration	Has two or more signs, there is some dehydration	There is severe dehydration
4. Treatment plan	Treatment Plan A	Treatment Plan B	Treatment Plan C



**TABLE 2: Clinical signs of dehydration.**

Body weight loss %	Clinical state	Signs
<5	Normal	<ul style="list-style-type: none"> <li>• Thirst</li> <li>• Dry mucous membrane</li> </ul>
5–10	Lethargy	<ul style="list-style-type: none"> <li>• Sunken eyes or fontanelle</li> <li>• Reduced tissue turgor</li> <li>• Tachycardia</li> <li>• Oliguria</li> <li>• Lack of tears</li> </ul>
>10	Shock	<ul style="list-style-type: none"> <li>• Peripheral circulatory failure</li> <li>• Small pulse volume</li> <li>• Tachycardia</li> <li>• Diminished consciousness</li> <li>• Hypotension</li> </ul>

so similar as to make this impossible. Urine examination, blood culture, and cerebrospinal fluid (CSF) examination may be indicated.

In children with acute watery diarrhea without fever, and some or no signs of dehydration no investigations are required. Microscopic examination of the stool is probably the only essential investigation in these children. Children who require hospitalization (high fever, toxic appearance, moderate to severe dehydration) require the following investigations.

#### LABORATORY SALIENT FINDINGS

- *Acid-base status:* Plasma electrolytes, urea and glucose
- *Microbiology of stools:* Microscopy and culture
- Urine examination
- Blood culture
- Cerebrospinal fluid (CSF) examination

## TREATMENT

The two main objectives in the management of acute diarrhea are:

1. Prevention of dehydration and providing nutritional support
2. Treatment of dehydration if present

These objectives can be achieved by following the treatment plans as described.

The broad principles of management of acute gastroenteritis in children include oral rehydration therapy, enteral feeding and diet selection, zinc supplementation, and additional therapies such as probiotics.

### Plan A: No Dehydration

#### Fluids

*Home available fluids:* Children with no signs of dehydration can be managed at home with

some available fluids (HAF). The home available fluids are rice water, dal water, lassi or buttermilk, coconut water, lemon water and plain water. The child is encouraged to take as much fluid as possible. Soft drinks, sweetened fruit drinks and tea are unsuitable and could be potentially dangerous.

*Sugar salt solution (SSS):* A homemade solution (sugar salt solution, made by adding two finger pinch of salt and one heaped teaspoon of sugar to 200 mL of water) is effective and a simple form of replacement solution. Limitations of SSS are uncertain availability of sugar, lack of suitable utensils for measuring ingredients and water and the difficulty in educating mothers to learn, retain and use the skills required for its proper preparation and administration.

#### Feeding during Diarrhea

Breastfeeding should always be continued during acute diarrhea. If the baby is on top milk then, animal milk need not be diluted with water during any phase of acute diarrhea. Feeding during diarrhea may increase the frequency of stool but does not worsen diarrhea nor increase the risk of dehydration. On the other hand, continued feeding during diarrhea facilitates mucosal recovery and may help in maintaining the nutritional status and preventing persistent diarrhea.

Older children who are not on breast milk should continue taking nutrient rich food which are available at home such as cereals mixed with milk. The rationale behind continued and aggressive feeding is that the overall nutrient absorption continues to be 70% during acute diarrhea.

Feeding therefore hastens repair of the intestinal mucosa and stimulates early recovery of the pancreatic function and production of brush border enzymes. Studies have shown that the weight gain after 8 days of starting treatment was greatest in those children receiving 110 kcal/kg/day throughout their illness as compared to those who have received 55 kcal/kg/day.

#### Oral Rehydration Therapy

Oral rehydration therapy (ORT) plus home available fluids (HAF) is called as ORT. The HAF are dal water, soup, buttermilk, coconut water and rice kanji. This should be encouraged as early as possible.

Children, especially infants, are more susceptible than adults to dehydration because of the greater basal fluid and electrolyte requirements per kilogram and because they are dependent



on others to meet these demands. Dehydration must be evaluated rapidly and corrected in 4–6 hours according to the degree of dehydration and estimated daily requirements. A small minority of children, especially those in shock or unable to tolerate oral fluids, require initial intravenous rehydration, but oral rehydration is the preferred mode of rehydration and replacement of ongoing losses.

Risks associated with severe dehydration that might necessitate intravenous resuscitation include: age <6 months; prematurity; chronic illness; fever >38°C (100.4°F) if younger than 3 months or >39°C (102.2°F) if 3–36 months of age; bloody diarrhea; persistent emesis; poor urine output; sunken eyes; and a depressed level of consciousness.

The low-osmolality oral rehydration should be given to infants and children slowly, especially if they have emesis. It can be given initially by a dropper, teaspoon, or syringe, beginning with as little as 5 mL at a time. The volume is increased as tolerated. Oral rehydration can also be given by nasogastric tube if needed; this is not the usual route.

Limitations to oral rehydration therapy include shock, an ileus, intussusception, carbohydrate intolerance (rare), severe emesis, and high stool output (>10 mL/kg/h). Ondansetron (oral mucosal absorption preparation) reduces the incidence of emesis, thus permitting more effective oral rehydration and is well established in emergency management of acute gastroenteritis in developed countries.

### Composition of ORS

World Health Organization (WHO) oral rehydration solution (ORS) containing 75 mEq of sodium, 64 mEq of chloride, 20 mEq of potassium, and 75 mmol of glucose per liter, with total osmolality of 245 mOsm/L, is now the global standard of care and more effective than home fluids.

The high sodium content is appropriate in cholera but may not be justified in noncholera diarrhea. This high sodium could result in hypernatremia especially in infants and neonates with diarrhea. Various measures to reduce the sodium load are:

- Lower sodium content in ORS
- Alternating breast milk and ORS (2:1)
- Diluting ORS in 1.5 L of water instead of 1 L. This is not scientifically approved as  $K^+$  and  $HCO_3^-$ —also get diluted.

**Glucose:** Optimal reabsorption of water and  $Na^+$  occur in the lumen when glucose and sodium are

in equimolar proportion. Formulas containing more glucose become hyperosmolar and induce osmotic diarrhea, thus making ORS solution dehydrating rather than rehydrating. The standard WHO ORS recommends 20 g/L of glucose providing 111 mmol/L.

**Potassium:** The concentration of  $K^+$  in ORS is 20 mEq/L. This reflects the  $K^+$  concentration in various forms of diarrhea. This concentration cannot be decreased further.

**Base:** Base replacement is in the form of citrate or bicarbonate in quantity sufficient to correct mild acidosis which occurs due to dehydration or stool bicarbonate losses.

**Osmolarity:** The effective osmolality should be similar or slightly less than plasma (220–310 mOsm).

The dose of ORS is 50–75 mL/kg in first 4 hours (Plan B).

### Maintenance Dose of ORS (Table 3)

After correction of dehydration ORS is given 50–100 mL/kg in 24 hours in between feeds. The ongoing losses can be corrected by giving 10 mL/kg for every stool. As easy formula is twice the weight of child in teaspoons, e.g., 5 kg child give 10 tsp (50 mL).

### Guidelines for Administration

ORS should be given only with tumbler and spoon at the rate of 1–2 tsp per minute, if child vomits, wait for 10 minutes and restart. If vomiting persists, place nasogastric tube and administer through the tube.

### Limitations of ORS

**WHO ORS:**

- Does not decrease the volume of diarrhea
- Does not stop diarrhea
- Does not decrease frequency

**TABLE 3:** WHO guidelines for ORS in children with no dehydration (Plan A).

Age	Quantity to be offered after each loose stool
<6 months	Quarter glass or cup (50 mL)
7 months to 2 years	Quarter to half glass or cup (50–100 mL)
2–5 years	Half to one glass or cup (100–200 mL)
Older children	As much as the child can take
ORS in Plan A is optional	

## Plan B: Some Dehydration (Mild to Moderate) (Table 4)

*Moderate (5% dehydration: vomiting not severe):* It is important to restore and maintain normal hydration. Frequent reassessment is advisable. Vomiting is usually transient. Small frequent feeds or nasogastric drip of oral rehydration fluids is usually retained.

### Fluids

When there is some dehydration the fluid deficit can be calculated as per the WHO guidelines. ORS is offered at the rate of 75 mL/kg over 4 hours. In children where the weight is not known the child's age can be used to determine the volume required although this is less precise.

Breastfeeding should be continued whatever be the degree of dehydration. Infants less than 6 months who are not breastfed, 100–200 mL of water should be given in addition to ORS during this period. Free access to plain water for older children should be made. If the child's eyelid becomes puffy, ORS is stopped and plain water or breast milk is given instead. ORS is given according to Plan A once the puffiness subsides.

*After 4 hours:* The child is reassessed and if there are no signs of dehydration, Plan A is followed and if signs of dehydration persist Plan B is repeated. Meanwhile food and milk are offered as mentioned in Plan A. If signs of severe dehydration appear, the management is shifted to Plan C.

### Maintenance Dose of ORS

50–100 mL/kg in 24 hours is given between feeds. For ongoing losses, ORS in the dose of 20–50 mL/kg/day or 10 mL/kg after each loose stool, should be given.

Breastfeeding should be continued, but cow milk feeds should be withheld for 6–12 hours (while rehydration is being achieved) and an

electrolyte and sugar solution given by mouth or by nasogastric tube. Avoid prolonged periods (>24 hours) of clear fluids or diluted milk feeds. Especially in malnourished children once rehydrated, milk feeds are restarted and can be given as full-strength feeds in amounts smaller than usual. Oral electrolyte and sugar solution is continued, but by 24 hours full volume (i.e., 150 mL/kg) full strength milk feeds should begin.

For children presenting with clinical signs of dehydration, therapy should be aimed at first correcting the fluid deficit and then maintaining hydration by replacing ongoing losses while maintaining nutrition. Correction of fluid deficits: can usually be accomplished via oral administration of appropriate glucose electrolyte solutions. Intravenous fluid therapy is required in only a small number of cases in which there is an accompanying ileus or the vomiting is of such magnitude that oral therapy fails: The fluid deficit is calculated on the basis of the clinical degree of dehydration and should provide 50 mL/kg body weight for mild dehydration (5%) and 100 mL/kg body weight for moderate dehydration (10%). The calculated deficit volume should be replaced over a period of 4–6 hours by offering frequent small volumes from a bottle, cup, or spoon, or it can be delivered as a continuous slow-rate infusion via a nasogastric tube. Once the child is fully rehydrated, the process of providing fluids to maintain hydration should begin, and the child should be encouraged to resume regular feedings.

## Plan C (Severe Dehydration) (Table 5)

*Severe (5–10% dehydrated and/or serious vomiting):* Requires intragastric drip of electrolyte/sugar solutions, but intravenous fluids are necessary if the patient suffers from shock, ileus, or severe vomiting. Refer the child to a hospital for treatment.

Children with moderate to severe dehydration who also have clinical findings of shock require urgent therapy to reestablish an adequate circulating blood volume. Fluid resuscitation in these cases requires intravenous administration of an isotonic crystalline solution such as normal saline. An initial rapid infusion of 20 mL/kg body weight of normal saline will correct the shock in most children with dehydration due to diarrhea. In those with persistent clinical signs of shock, a second infusion of 20 mL/kg body weight can be administered. After the child's circulatory compromise has been corrected, the process of rehydration with maintenance therapy and early reintroduction of feeds as outlined previously.

**TABLE 4: WHO guidelines for ORS in children with some dehydration (Plan B).**

Age	Weight (kg)	ORS (mL)	Glass
<4 months	<5 kg	200–400	1–2
4–11 months	5–7.9 kg	400–600	2–3
12–23 months	8–10.9 kg	600–800	3–4
2–4 years	10–15.9 kg	800–1200	4–6
5–14 years	16–29.9 kg	1200–2200	6–11
>15 years	30 kg or more	>2200	12–20

**TABLE 5: Intravenous fluid therapy in severe dehydration.**

	<i>First give 30 mL/kg in</i>	<i>Then give 70 mL/kg in</i>
<1 year of age	1 hour*	5 hours
Older children	30 minutes	2 ½ hours

\*Repeat again if the radial pulse is still very weak or not detectable

Intravenous fluids are started immediately. While the drip is being set, ORS solution is offered if the child can drink. The best IV fluid solution is Ringer's lactate solution. An ideal preparation would be Ringer's lactate with 5% dextrose. If plain Ringer's lactate is also not available, normal saline solution (0.9% NaCl) can be used. Plain dextrose solution is not effective.

All children should be started on some ORS solution (about 5 mL/kg/h) when they can drink while on IV fluids (usually within 3–4 hours for infants or 1–2 hours for older children). If IV line is not accessible, rehydration is done with ORS using NG tube at 20 mL/kg/h (total of 120 mL/kg). The child is reassessed every 1–2 hours and the fluid is decreased if there is repeated vomiting or abdominal distension. If there is no improvement in hydration after 3 hours, IV fluids should be restarted, as early as possible.

## General Recommendations for IV Fluid Therapy

Children with diarrhea with or without vomiting would require intravenous fluid therapy, if there is:

- Severe dehydration with or without shock
- Persistent vomiting (more than 3 per hour)
- Failure to correct or worsening of dehydration on ORT
- High purge rate (would get reflected in persistent dehydration)
- Failure of acceptance of ORS in dehydration child
- Abdominal distension
- Deranged sensorium

Children presenting with shock and/or other features of severe dehydration should be given IV fluids rapidly. Ringer's lactate is preferable for initial therapy in these children as it provides extra sodium and also helps to correct acidosis, which is often present in such children.

These children should be given 20–30 mL/kg of Ringer's lactate as rapid infusion (within ½ to 1 hour). This may be repeated if the child's pulse

is still feeble or the child has failed to pass urine. Thus, these children can receive 50–60 mL/kg within 2 hours of admission. If the urination is established by this time, then the remaining amount (90–100 mL/kg) of IV fluids required for correction of severe dehydration could be given over next 6 hours as half strength (N/2) saline.

If there is failure to pass urine even after 50–60 mL/kg of Ringer's lactate in two hours, then the child should be assessed for possible renal failure due to acute tubular necrosis. For this, the child's hydration status should be assessed.

If the child is still dehydrated, he should be given more fluids, but if he appears well hydrated with good pulse, then he should be given IV furosemide (1–2 mg/kg/IV stat) to force diuresis.

If the child still fails to pass urine despite furosemide, then a diagnosis of ATN is established and the child should be managed on line of acute renal failure. It is very important that furosemide test be given only when the child is clinically well and hydrated.

As mentioned above, IV fluids should be given for the shortest possible time. Most children can be started on ORT after correction of dehydration. Some children may still require IV fluid therapy, either because of inadequate intake of ORS or because of complications like abdominal distension, deranged sensorium or convulsions.

These children should then be shifted to IV maintenance fluid therapy. Maintenance fluids are given as N/4 saline ( $\text{Na}^+$  37.5 mEq/L) in children less than 3 months of age or as N/6 saline ( $\text{Na}^+$  25 mEq/L) in children less than 3 months of age. Maintenance fluids must contain  $\text{K}^+$  in the concentration (20 mEq/L).

## Management of Electrolyte Disturbance

### Hyponatremia

This is the most frequent electrolyte disturbance seen in children with diarrhea and vomiting. About 30–35% of children at the time of admission may have serum sodium <135 mEq/L. But severe hyponatremia ( $\text{Na}^+ < 125$  mEq/L) is not common.

**Correction of hyponatremia:** Deficit fluid therapy given with either N/2 saline or with Ringer's lactate is usually sufficient to correct mild to moderate hyponatremia ( $\text{Na}^+$  125–135 mEq/L) in most children. However, if the child is symptomatic (having convulsion) and his serum  $\text{Na}^+$  is less than 125 mEq/L then he or she would require more rapid correction of serum sodium. Amount of  $\text{Na}^+$

required to correct deficit can be calculated by the following formula:

Amount of  $\text{Na}^+$  required =  $\text{Na}^+$  deficit in mEq/L  $\times$   $0.6 \times$  weight in kilogram.

### *Hypernatremia*

This is uncommon in clinical practice but does occur in western countries where children are largely given skimmed milk feeding, containing high amounts of sodium. Inappropriate mixing of ORS or sugar salt solution are probably the only important causes of hypernatremia dehydration.

If the child arrives in shock, the initial management is still with 20–30 mL/kg of Ringer's lactate till the shock is reversed. If hypernatremia is confirmed then the child is given fluids containing 50–60 mEq/L (N/3 saline) in just maintenance amounts. This enables hypernatremic dehydration to be corrected over 36–48 hours. More rapid correction is not desirable as it could lead to hyponatremic convulsions.

### *Hypokalemia*

Hypokalemia is frequently seen in malnourished children with diarrhea. It may be clinically asymptomatic or the child may have hypotonia (neck flop, pseudoparalysis, etc.) and abdominal distension due to paralytic ileus. Hypokalemia should be documented by measuring serum potassium.

Hypokalemia should be corrected very slowly. A mere increase in the concentration of KCl from 20 mEq/L to 30–40 mEq/L in the infusion fluid is sufficient to correct hypokalemia. Potassium should never be given in higher concentrations than 40 mEq/L.

### *Metabolic Acidosis*

This is also not uncommon. Most of the metabolic acidosis in diarrheal children occurs due to depletion of blood volume and consequent compromise of renal function. This is corrected with correction of dehydration and restoration of blood volume as well as renal plasma flow. Severe metabolic acidosis manifests as deep and fast breathing with plasma bicarbonate levels usually below 15 mEq/L.

Symptomatic metabolic acidosis should be corrected by giving 3 mL/kg of 7.5% sodium bicarbonate solution. This should be diluted 6 times with 5% dextrose. Total volume (20 mL/kg) of diluted bicarbonate should be given over half to one hour. This would usually increase serum

bicarbonate levels by 5–7 mEq/L. If plasma bicarbonate levels are available then actual amounts of bicarbonate required can be calculated as follows.

Amount of sodium bicarbonate required (in mEq) = Bicarbonate deficit (desired bicarbonate – actual bicarbonate) in mEq/L  $\times$   $0.6 \times$  weight in kilogram.

Correction is usually done only up to 18 mEq/L.

Once rehydration is complete, food should be reintroduced while oral rehydration is continued to replace ongoing losses from emesis or stools and for maintenance. Breastfeeding or nondiluted regular formula should be resumed as soon as possible. Foods with complex carbohydrates (rice, wheat, potatoes, bread, and cereals), lean meats, yogurt, fruits, and vegetables are also tolerated. Fatty foods or foods high in simple sugars (juices, carbonated sodas) should be avoided, the usual energy density of any diet used for the therapy of diarrhea should be around 1 kcal/g, aiming to provide an energy intake of a minimum of 100 kcal/kg/day and a protein intake of 2.3 g/kg/day, in selected circumstances when adequate intake of energy-dense food is problematic, the addition of amylase to the diet through germination techniques can also be helpful.

With the exception of acute lactose intolerance in a small subgroup, most children with diarrhea are able to tolerate milk and lactose containing diets. Withdrawal of milk and replacement with specialized (and expensive) lactose-free formulations are unnecessary. Although children with persistent diarrhea are not lactose intolerant, administration of a lactose load exceeding 5 g/kg/day may be associated with higher purging rates and treatment failure. Alternative strategies for reducing the lactose load while feeding malnourished children who have prolonged diarrhea include addition of milk to cereals and replacement of milk with fermented milk products such as yogurt.

Lactose intolerance is an important complication in some cases, but even among those children for whom lactose avoidance may be necessary, nutritionally complete diets comprised of locally available ingredients can be used at least as effective, as commercial preparations or specialized ingredients.

### **Drug Therapy in Diarrhea**

More than 90% of cases of acute diarrhea (simple diarrhea) do not require antibiotics, however antibiotics are frequently prescribed. Antibiotics can

induce bacterial resistance and chronic carrier stage and cause disequilibrium of intestinal ecosystem facilitating growth of pathogenic opportunistic organisms such as the anaerobic *C. difficile*.

Antibiotics are of no proven efficacy on duration or severity of illness or the risk of complications in a wide variety of organisms ranging from viruses to some enteroinvasive bacteria like *Salmonella* and parasites like *Cryptosporidium*.

The definite clinical indications of antibiotics are:

- *Shigella* dysentery, Giardiasis, infection with *E. histolytica*
- Cholera
- Septicemia/Toxemia/diarrhea due to systemic illness
- Young infants with toxemia
- Moderate to severe protein-calorie malnutrition
- Immunocompromised situations

The value of antibiotics can be classified usefully as:

- High: *Shigella*, *V. cholerae*, *Giardia*, *E. histolytica*
- Questionable: *Campylobacter*, *Yersinia*, *E. coli*
- No value: *Salmonella*, viruses

Antibiotics generally are not recommended for children presenting with acute bloody diarrhea unless a specific pathogen has been isolated. Antibiotics are indicated in immunocompromised children or those with septicemia due to *Salmonella*, *Campylobacter*, or *Yersinia*. In patients with diarrhea due to enterohemorrhagic *E. coli*, antibiotic therapy has been implicated as a risk factor for the subsequent development of hemolytic uremic syndrome. Confirmed shigellosis and cholera should be treated with an antibacterial drug. Depending on local sensitivities, trimethoprim/sulfamethoxazole or ampicillin may be used for shigella and azithromycin is most effective in children with cholera. Some probiotic supplements have been shown to decrease the duration of the acute diarrheal illnesses. Probiotics may exert an immunomodulatory on the host and static effect on some enteropathogens, thereby altering the intestinal microflora. *Saccharomyces boulardii*, nonpathogenic yeast has been used to treat and decrease the recurrence rate of *C. difficile* enterocolitis, and *Lactobacillus rhamnosus* GG may lessen the severity of rotaviral dehydration. Zinc is recommended as an adjunct to ORT in low-income countries. However, its efficacy in nonmalnourished children is not supported by solid evidence.

## Bacterial Infections

- *Shigella dysentery*: Antibiotics shorten duration of illness, reduce excretion of organisms and reduce secondary attack rates in shigella dysentery. However, they may increase bacterial resistance and are sometimes responsible for the hemolytic uremic syndrome (HUS) like sequelae. Trimethoprim-Sulfamethoxazole is generally the first choice among antibiotics, but has recently lost its sensitivity in most parts of our country and hence local sensitivity patterns must be considered when choosing antibiotics. Nalidixic acid, Norfloxacin and ciprofloxacin are useful alternatives and have proven fairly safe for use in children. Course treatment with ofloxacin or cefixime has also been found to be useful both in efficacy and cost effectiveness.
- *Vibrios (Cholera)*: Antibiotics make a significant difference in outcome and spread of cholera and have been listed, by WHO as 'clearly indicated'. Antibiotic of choice is Doxycycline (short courses do not cause major toxicity even in children less than 8 years of age).
- *E. coli*: These are the most commonly grown organisms in stool cultures. However, serotyping is rarely carried out in our country and therefore, the pathogenicity is always questionable. Enteropathogenic *E. coli* (EPEC) is commonly associated with acute watery diarrheas of infants and young children in developing countries and may be associated with significant morbidity. Antibiotics, e.g., TMP-SM combination may be used in those with signs of toxicity. Enterotoxigenic *E. coli* (ETEC) is also a common cause of simple watery diarrheas and usually requires only supportive management. 'Traveler's diarrhea' with ETEC however should be treated with TMP-SM or Norfloxacin or Furazolidone. Antibiotics are not useful in EIEC or EHEC types of *E. coli*.
- *Salmonella*: Diarrheas are usually mild, watery and self-limited. Antibiotics are clearly responsible for increased carrier stage. However, they are recommended occasionally in toxic or immunocompromised infants with septicemia.

## Protozoal Infections

Drugs are clearly indicated in diarrheas due to *G. lamblia*. *E. histolytica* is not a common cause



of dysentery in children. However, treatment may be necessary for diarrheas associated with trophozoite forms and in complications of amebiasis. Although microsporidia and *Isospora* are generally amenable to antimicrobials, cryptosporidium is particularly difficult to treat and antibiotics are largely ineffective. These organisms however are usually (but not always) associated with immunocompromised states (such as HIV) and outcome depends mainly on management of primary condition.

## Zinc Therapy

Zinc supplementation in children with diarrhea in developing countries leads to reduced duration and severity of diarrhea and could potentially prevent a large proportion of cases from recurring. Zinc administration for diarrhea management can significantly reduce all-cause mortality. In addition to improving diarrhea recovery rates, administration of zinc in community settings leads to increased use of ORS and reduction in the inappropriate use of antimicrobials. All children older than 6 months of age with acute diarrhea in at-risk areas should receive oral zinc (20 mg/day) in some form for 10–14 days during and continued after diarrhea.

## Probiotics

The use of probiotic nonpathogenic bacteria for prevention and therapy of diarrhea has been successful in some settings although the evidence is inconclusive to recommend their use in all settings. In addition to restoring beneficial intestinal flora, probiotics can enhance host protective immunity such as down regulation of proinflammatory cytokines and upregulation of anti-inflammatory cytokines. *Saccharomyces boulardii* is effective in antibiotic-associated and in *C. difficile* diarrhea, and there is some evidence that it might prevent diarrhea in daycare centers. *Lactobacillus rhamnosus* GG is associated with reduced diarrheal duration and severity, which reduction is more evident in cases of childhood rotavirus diarrhea.

*Saccharomyces boulardii* and *Lactobacillus* GG are the only nonbacterial biotherapeutic agents with systematic convincing data from double blind studies against prevention and treatment of acute diarrhea and antibiotic associated diarrhea. The results of most prospective double blind clinical trials with other bacterial biotherapeutic agents are disappointing showing a lack of efficacy.

## Antisecretory Drug: Racecadotril

Racecadotril is an enkephalinase inhibitor that reduces intestinal hypersecretion by inhibiting this intestinal enzyme. Racecadotril prevents the inactivation of endogenous act as neurotransmitters in the GIT by activating opiate receptors and thus reducing the levels of cAMP. This results in the reduced secretions of water and electrolytes without any effects on intestinal motility. Racecadotril has antisecretory effects only when hypersecretion is present and not in the basal state, unlike loperamide. It also does not produce constipation, bacterial overgrowth or toxic megacolon so often seen with loperamide.

It is given in a dose of 1.5 mg/kg body weight every 8 hours. There are transient and mild side effects. Impact of this drug will be significant in developing countries, as it will reduce the stool output during diarrhea.

## Nutrition in Diarrhea

In acute diarrhea, the presence of malnutrition is an important triggering event for progression to persistent diarrhea. Diet in diarrhea, therefore, forms a crucial component in therapy and should be balanced in such a way as to supply adequate calories and nutrients and at the same time not worsen the pre-existing villous injury.

## Rotavirus Immunization

Most infants acquire rotavirus diarrhea early in life; an effective rotavirus vaccine would have a major effect on reducing diarrhea mortality in developing countries.

It is now clear that the introduction of these vaccines is associated with a significant reduction in severe diarrhea and associated mortality.

Other vaccines that could potentially reduce the burden of severe diarrhea and mortality in young children are vaccines against cholera, *Shigella*, and ETEC. Preventive use of cholera vaccines in endemic countries can reduce the risk of developing cholera.

## COMPLICATIONS OF DIARRHEA

The common complications of acute watery diarrhea are:

- Dehydration
- Dyselectrolytemia
- Precipitation of malnutrition
- Secondary lactose intolerance
- Prolongation of diarrhea—persistent diarrhea
- Toxic ileus



- Hemolytic uremic syndrome
- Disseminated intravascular coagulation
- Cortical vein thrombosis

## FOLLOW-UP ADVICE

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Children with acute diarrhea should continue the nutritional advice and utmost care should be taken to prevent another episode of diarrhea. Detailed advice regarding immunization should also be given to the parents.

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## PRESENTING COMPLAINTS

A 6-year-old boy was brought with the complaints of:

- Abdominal pain since 2 days
- Vomiting since 1 day
- Fever since 1 day

## History of Presenting Complaints

A 6-year-old boy presented with the history of abdominal pain of sudden onset. Abdominal pain was present around the umbilicus. There was no radiation of the pain. The pain was associated with vomiting. Vomiting was of insidious type. Child had vomited 4–5 times since last 12 hours. Vomiting contained ingested food material. It was non-bilious. Abdominal pain was associated with fever. Fever was moderate-to-high degree and was relieved after taking paracetamol. Fever was not associated with chills and rigors.

### CASE AT A GLANCE

#### Basic Findings

Height	: 116 cm (70th centile)
Weight	: 18 kg (50th centile)
Temperature	: 35°C
Pulse rate	: 118 per minute
Respiratory rate	: 22 per minute
Blood pressure	: 100/70 mm Hg

#### Positive Findings

##### History

- Abdominal pain
- Vomiting
- Fever
- Crying and irritability

##### Examination

- Tenderness
- Guarding

##### Investigation

- TLC: Increased
- DLC: Neutrophils increased
- Urine: Pus cells present

## Past History of the Patient

The boy was the second sibling of nonconsanguineous marriage. He was born at full term with assisted normal delivery. He cried immediately after the delivery. There was no significant post-natal event. His birth weight was 3.25 kg. He was on breast milk for the first 3 months, later weaning was started and completed by 18 months. His developmental milestones were normal. He was immunized completely. His school performance was good. He was maintaining good health except for the minor on and off abdominal pain.

## EXAMINATION

On examination, the boy was moderately built and nourished. Child was in agony with the abdominal pain. Child was comfortable, when he was placed prone with the right lower limb flexed up at hip. Anthropometric measurements included the height 116 cm (70th centile), the weight was 18 kg (50th centile).

He was febrile, 38°C and his pulse rate was 118 per minute. The respiratory rate was 22 per minute. The blood pressure recorded was 100/70 mm Hg.

He looked pale. There was no cyanosis, no icterus and no lymphadenopathy. Per abdomen examination revealed the presence of diffuse periumbilical and right iliac fossa tenderness. Mild guarding was present. There was no rebound tenderness. There was no organomegaly. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 7 g/dL
TLC	: 17,500 cells/cu mm
DLC	: P <sub>72</sub> L <sub>22</sub> E <sub>3</sub> M <sub>3</sub>
ESR	: 20 mm in the 1st hour
Plain X-ray abdomen	: Presence of the fecalith in ileum
X-ray chest	: Normal
Urine microscopy	: 10–12 pus cells/HPF

## DISCUSSION

Appendicitis is the most common condition requiring emergency abdominal surgery in childhood. The incidence of appendicitis increases with the age. It is more common among the adolescence and less common among the younger than 1 year. Boys are more affected. The risk of perforation is greatest in 1–4-year-old children. Children have a higher perforation rate than adults and up to 10% of children present with complicated disease.

## PATHOLOGY

Appendicitis is classically believed to be secondary to obstruction of the appendiceal orifice, commonly either by a fecalith or lymphoid hyperplasia after viral illness. Other causes of obstruction include parasites and tumors. It is associated with infection. One pathway to acute appendicitis begins with luminal obstruction; inspissated fecal material, lymphoid hyperplasia, ingested foreign body, parasites, and tumors have been implicated. Obstruction of the vermiform appendix leads to a closed loop, with mucus production, bacterial overgrowth, and resultant distention.

Luminal obstruction leads to progressive cascade including increasing intraluminal pressures from bacterial proliferation and continued secretion of mucus, elevated intraluminal pressure, lymphatic and venous congestion and edema, impaired arterial perfusion, ischemia of the wall of the appendix, bacterial invasion of the appendiceal wall and necrosis. This occurs through all the layers of the appendiceal wall. Finally necrosis of wall results in perforation and contamination of the peritoneum. The perforation usually occurs at the tip of the appendix distal to obstruction to fecolith. Bacterial invasion of the mesenteric vein may result in portal vein sepsis and subsequent liver abscess. The inflammatory process associated with perforation may lead to intestinal obstructions or paralytic ileus. This progression correlates with the clinical disease progression from simple appendicitis to gangrenous appendicitis and, thereafter, appendiceal perforation. Fecaliths and appendicitis are more common in developed countries with refined, low-fiber diets than in developing countries with a high-fiber diet.

Enteric infection likely plays a role in many cases in association with mucosal ulceration and invasion of the appendiceal wall by bacteria. Bacteria such as *Yersinia*, *Salmonella* and *Shigella*, and viruses such as infectious mononucleosis, mumps, coxsackievirus B, and adenovirus are implicated. Carcinoid tumor, foreign bodies,

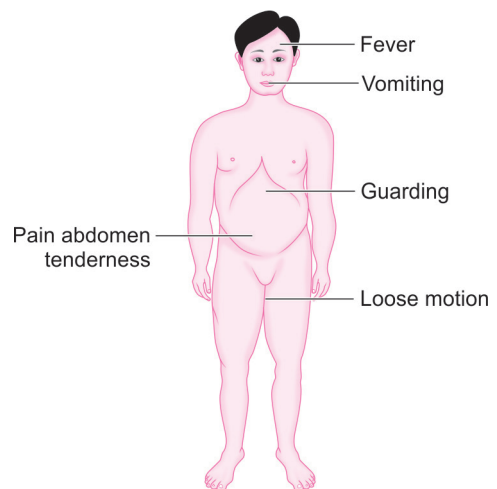
ascariasis have been implicated as the cause of obstruction. Abnormal mucus has been the cause of obstruction in cystic fibrosis.

As the inflammation progresses to involve serosa and overlying peritoneum, pain migrates to areas of the peritoneal irritation usually right lower quadrant. With the perforations pain becomes generalized. The progression from the onset of the symptoms to perforation usually occurs over 36–48 hours. Young children will have poorly developed omentum. As a consequence to perforation, organisms may not be confined to right iliac fossa as in adult, hence it will spread throughout the peritoneal cavity.

## CLINICAL FEATURES (FIG. 1)

Appendicitis is the most common in older children, with peak incidence between the ages of 12 and 18 years; it is rare in children younger than 5 years of age (<5% of cases) and extremely rare (<1% of cases) in children younger than 3 years of age. It affects boys slightly more often than girls. There is a seasonal peak incidence in autumn and spring. Perforation in appendicitis is more common in children compared to adults, particularly in young children; with perforation rates as high as 82% for children younger than 5 years.

History favoring a diagnosis of appendicitis include onset of pain before the vomiting or diarrhea, loss of appetite, migration of pain from periumbilical region to right iliac fossa. Untreated appendicitis proceeds to the perforation within 48–72 hours. Therefore duration of symptoms is important in the interpretation of the signs and in determining the treatment strategy.



**Fig. 1:** Clinical features.

Clinical signs and symptoms depend upon pathological phase of the illness. The classical triad is pain, vomiting, and fever. In the beginning, pain will be confined to periumbilical region. Later, it will be associated with nausea and vomiting.

The majority of cases of appendicitis have an “atypical” presentation. The illness typically begins insidiously with a brief (several hours) period of generalized malaise and anorexia; the child does not appear ill. The illness escalates rapidly with progressive abdominal pain followed by vomiting, and appendiceal perforation is likely to occur within 48 hours of the onset of illness. The diagnosis before perforation in acute appendicitis in children is generally brief 36–48 hours.

Abdominal pain is consistently the primary and often the first symptom; beginning shortly (hours) after the onset of illness. As with other visceral organs, there are no somatic pain fibers within the appendix; therefore, early appendiceal inflammation results in pain which is vague, poorly localized, unrelated to activity or position, often colicky, and periumbilical in location as a result of visceral inflammation from a distended appendix. Progression of the inflammatory process in the next 12–24 hours leads to involvement of the adjacent parietal peritoneal surfaces, resulting in somatic pain localized to the RIF. The position of the appendix is a critical factor affecting interpretation of presenting signs and symptoms and accurate diagnosis. The pain becomes steady and more severe and is exacerbated by movement.

McBurney point is the junction of the lateral and middle third of the line joining the right iliac, suprailiac spine and the umbilicus. The most important physical finding is persistent direct tenderness to the palpation, and the rigidity of the overlying rectus muscle. However, if the diagnosis is doubtful especially in a very young child, less than 5 years rectal examination, reveals important information. Localized tenderness is a later and less-consistent finding when the appendix is retrocecal in position (>50% of cases). In cases of an appendix localized entirely in the pelvis, the tenderness on abdominal examination may be minimal and best appreciated on rectal examination. Later careful examination should be performed to diagnose shock as a result of sepsis and dehydration or both.

Nausea and vomiting occur in more than half the patients, and usually follow the onset of abdominal pain by several hours. Anorexia is a classic and consistent finding in acute appendicitis. Fever is common and typically low-grade unless perforation has occurred. Most patients demonstrate at least mild tachycardia.

The temporal progression of symptoms from vague, mild pain, malaise, and anorexia to severe localized pain, fever, and vomiting typically occurs rapidly, in 24–48 hours in the majority of cases. If the diagnosis is delayed beyond 36–48 hours, the perforation rate exceeds. If perforation leads to diffuse peritonitis, the child generally has escalating diffuse abdominal pain and rapid development of toxicity evidenced by dehydration and signs of sepsis including hypotension, oliguria, acidosis, and high-grade fever. When several days have elapsed in the progression of appendicitis, patients often develop signs and symptoms of developing small bowel obstruction. If the appendix is retrocecal, then the appendicitis predictably evolves more slowly and patients are likely to relate 4–5 days of illness preceding evaluation. The pain is typically more lateral and posterior, and can mimic the symptoms associated with septic arthritis of the hip or a psoas muscle abscess.

Examination findings must be interpreted relative to the temporal evolution of the illness. Abdominal tenderness may be vague or even absent early in the course of appendicitis and is often diffuse after rupture.

Rebound tenderness and referred tenderness (Rovsing sign) are also consistent findings in acute appendicitis but not always present. Rebound tenderness is elicited by deep palpation of the abdomen followed by the sudden release of the examining hand. This is often very painful to the child and has demonstrated poor correlation with peritonitis, so it should be avoided. Gentle finger percussion is a better test for peritoneal irritation. Similarly digital rectal examination is uncomfortable and unlikely to contribute to the evaluation of appendicitis in most cases of appendicitis in children.

#### ESSENTIAL DIAGNOSTIC POINTS

- Obstruction of the lumen is the primary cause of appendicitis.
- Most common condition requiring emergency abdominal surgery.
- The obstruction is mainly caused by fecaliths.
- Infective agents may be *Yersinia*, *Salmonella* and *Shigella*.
- The classical triad is pain, vomiting, and fever.
- Rebound tenderness is tested by gentle finger percussion in all four quadrants in all the age groups.

Guarding may be present, and child may protect the area with the hand. Abdominal distension may suggest perforation or obstruction. The right lower quadrant, i.e., McBurney point should be palpated last.

Pelvic appendicitis produces rectal tenderness. Perforation leads to temporary relief of symptoms. Local muscular rigidity, psoas muscle spasms, rebound tenderness are present. Per rectal examination is painful in pelvic appendicitis.

Psoas and obturator internus signs are pain with passive stretch of these muscles. The psoas sign is elicited with active right thigh flexion or passive extension of the hip and typically positive in cases of a retrocecal appendix. The obturator sign is demonstrated by adductor pain after internal rotation of the flexed thigh and typically positive in cases of a pelvic appendix. Physical examination may demonstrate a mass in the RIF representing an inflammatory phlegmon around the appendix or a localized abscess (fluid collection).

#### GENERAL FEATURES

- Anorexia
- Rebound tenderness
- Persistent direct tenderness
- Abdominal rigidity over the rectal muscle

### INVESTIGATION

A child with a chief complaint of migrating periumbilical to right lower quadrant, abdominal pain, anorexia, right lower quadrant tenderness on examination, and leukocytosis is likely to have appendicitis. The differential diagnosis in a child with right lower quadrant abdominal pain includes both nonsurgical processes, such as enteritis, mesenteric adenitis, constipation, nephrolithiasis, inflammatory bowel disease especially Crohn disease, pneumonia, and urinary tract infections, and surgical processes, including intussusception and Meckel diverticulum.

The leukocyte count in early appendicitis may be normal and typically is only mildly elevated with a left shift (11,000–16,000/cu mm) as the illness progresses in the initial 24–48 hours. The leukocyte count may be markedly elevated (20,000/cu mm) in perforated appendicitis and rarely in nonperforated cases.

Urinalysis often demonstrates a few white or red blood cells, as a result of the proximity of the inflamed appendix to the ureter or bladder, but it should be free of bacteria.

C-reactive protein increases in proportion to the degree of appendiceal inflammation but is nonspecific and not widely used. Serum amyloid A protein is consistently elevated in patients with acute appendicitis.

### Plain Radiographs

Plain X-ray abdomen shows:

- Calcified appendicolith

- Gas fluid level in cecum
- Small bowel dilatation without fluid level
- Amputation of the gas at the hepatic flexure due to spastic ascending colon–colon cut-off sign
- Obliteration of right psoas shadow
- Pneumoperitoneum in case of peritonitis.

Barium studies shows:

- Absent or incomplete filling of the appendix
- Irregularities in the appendicular lumen

### Ultrasound

Ultrasonography demonstrates fecaliths, presence of intraluminal fluid and thickened appendiceal wall, i.e., more than 2 mm in thickness when the appendix ruptures, and the tip blows out the appendix becomes difficult to identify. The appendix is identified as a blind ending, tubular, non-peristalsing segment of the bowel arising from the cecum. A noncompressible appendix, periappendiceal inflammation, and presence of an appendicolith are described as reliable indicators of acute appendicitis. The diagnosis of appendicitis relies on visualizing a noncompressible appendix that is more than 6 mm in diameter, lack of compressibility, a complex mass in the RIF, or an appendicolith. Asymmetric thickening is also an indication of the inflammation. The visualized appendix usually coincides with the site of localized pain and tenderness. Findings that suggest advanced appendicitis on ultrasound include asymmetric wall thickening, abscess formation, associated free intraperitoneal fluid, surrounding tissue edema, and decreased local tenderness to compression.

When the patient presents with perforated appendicitis, the USG can yield free fluid in the abdomen or intra-abdominal abscess and possibly a free fecalith. In large children's hospitals, USG is routinely used as a first-line diagnostic modality.

### CT Scan

In the cases, where either the appendix cannot be identified or the diagnosis is still unclear, computed tomography (CT) has been advocated. CT removes the variable of operator skill and is not affected larger body habitus or overlying intraluminal bowel gas. However, CT introduces the risk of ionizing radiation and increased cost. Therefore, many practitioners advocate for the USG—first paradigm in the imaging for suspected appendicitis.

CT scan may be most useful in advanced appendicitis to identify and guide percutaneous

drainage of fluid collections and identification of an inflammatory mass, which might prompt a plan for initial nonoperative management.

CT scan findings include:

- Circumferential thickening of wall of appendix
- Phlegman—pericecal fat tissue
- Homogeneous ring-like calcification—appendicolith
- Linear streaky densities in pericecal/mesenteric pelvic fat.

#### LABORATORY SALIENT FINDINGS

- Leukocytosis and shift in differential count
- Urine analysis may show the presence of pus cells as well as red blood cells
- *Plain X-ray abdomen*: Calcified appendicolith gas fluid level in cecum
- *Barium studies*:
  - Absent or incomplete filling of the appendix
  - Irregularities in the appendicular lumen
- Ultrasonography demonstrates fecaliths, presence of intraluminal fluid and thickened appendical wall
- *CT scan*: Circumferential thickening of wall of appendix
  - Phlegman—pericecal fat tissue Homogeneous ring-like calcification—appendicolith

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes Crohn's disease, Meckel's diverticulum, mesenteric adenitis, urinary tract infection, hemolytic-uremic syndrome and Henoch-Schönlein purpura.

## COMPLICATIONS

Complications occur in 25–30% of children with appendicitis. Main complication is perforation. Appendicular abscess can also occur. Intra-abdominal abscess is rare. Liver abscess from the portal vein sepsis is common. Intestinal obstruction from the portal vein sepsis is common.

## TREATMENT

Once the diagnosis of appendicitis is confirmed or highly suspected, standard treatment for acute appendicitis is most often prompt appendectomy. Some reports suggest initial nonoperative management (antibiotics and drainage of fluid collections) as an alternative option in presentations, depending on the patient's general condition and state of the appendix.

To be considered uncomplicated, patients had pain <48 hours, ultrasonographic or CT documentation of a nonruptured appendix, as well as an appendiceal diameter <1.1 cm without phlegmon, abscess, or fecalith. Management included a minimum of 24 hours of

intravenous antibiotics (piperacillin-tazobactam or ciprofloxacin with metronidazole) followed by amoxicillin-clavulanate or ciprofloxacin with metronidazole to complete a 10-day total antibiotic course. The operation should proceed semi-electively within 12–24 hours of diagnosis. Children with appendicitis are typically at least mildly dehydrated and require preoperative fluid resuscitation to correct hypovolemia and electrolyte abnormalities before anesthesia. Fever, if present, should be treated. Pain management begins even before a definitive diagnosis is made. In the majority of cases, preoperative management can be accomplished during the period of diagnostic evaluation and prompt appendectomy can be performed.

## Antibiotics

Recently, the choice for antibiotic administration for appendicitis has come up for debate. Recent studies have compared the traditional triple antibiotic regimen (e.g., ampicillin, gentamicin, and clindamycin) to once-daily dosing of ceftriaxone and metronidazole and have not demonstrated a difference in outcome. Additionally, the use of oral antibiotics prior to postoperative day 5, if the patient is able to tolerate oral medications has become more popular. Further, once the leukocytosis has resolved, patients can be safely discharged home prior to completing 5 days of intravenous antibiotics.

Antibiotics substantially lower the incidence of postoperative wound infections and intraperitoneal abscesses in perforated appendicitis; but their role is less well defined in simple appendicitis. The antibiotic regimen should be directed against the typical bacterial flora found in the appendix, including anaerobic organisms (*Bacteroides*, *Clostridia*, and *Streptococcus* spp.) and gram-negative aerobic bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobacter*, and *Klebsiella*.

For simple nonperforated appendicitis, one preoperative dose of a single broad-spectrum agent (cefoxitin) or equivalent is sufficient. The practice in perforated or gangrenous appendicitis, most surgeons prefer combination regimens such as (piperacillin/tazobactam), ticarcillin/clavulanate, or ceftriaxone/metronidazole. The traditional triple antibiotic regimen (ampicillin, gentamicin, and clindamycin or metronidazole) is still effective, but adds cost and has the concern for ototoxicity. The commonly used antibiotics are ampicillin (100 mg/kg/24 h), gentamicin (5 mg/kg/24 h), and clindamycin (30 mg/kg/24 h),



cefataxim (50–100 mg/kg/24 h), and ceftriaxone (50–100 mg/kg/24 h).

Antibiotics should be given for 7–10 days and is continued postoperatively for 3–5 days. Oral antibiotics are equally as effective as intravenous, and therefore the patient can be switched to an oral regimen and discharged once bowel function returns. This transition to oral antibiotics has significantly affected length of stay and cost in the management of perforated appendicitis.

## Surgery

Diagnostic laparoscopy and laparoscopic appendectomy (minimally invasive technique) for both simple and perforated appendicitis are the preferred approaches in most pediatric centers; the open surgery is still performed in selected cases. Laparoscopic appendectomy has significant advantages in administrative factors (cost, resource utilization, length of stay) and slight improvement in clinical outcome measures (wound infection rate, intra-abdominal abscess, analgesic requirements, return to full activity), but have failed to establish an evidence-based preference between laparoscopic and open appendectomy in children. In nonperforated appendicitis, laparoscopic appendectomy appears to have lower narcotic analgesic requirements, decreased wound morbidity, and improved cosmesis, but operative times seem slightly higher and costs are almost doubled compared to the open procedure. Length of hospitalization is similar for both approaches.

The role of laparoscopy in perforated appendicitis is less well-defined. There are no convincing data to recommend one approach in all patients. Most pediatric surgeons use both approaches selectively. The laparoscopic approach is used most often for obese patients, when alternative diagnoses are suspected, and in adolescent girls to better evaluate for ovarian pathology and pelvic inflammatory disease while avoiding the ionizing radiation associated with CT imaging.

Nasogastric suction should be done if there is vomiting and abdominal distension. In children with unperforated appendicitis, intravenous fluid and antibiotics should be started. Treatment in perforated appendix range from non-surgical to aggressive surgical resection with antibiotic irrigate, drainage of peritoneal cavity of even delayed wound closure. Appendiceal mass is treated with initial conservative regimen, followed by interval appendectomy in 4–8 weeks.

## Complications

The most common complications are wound infections and intra-abdominal abscesses; both are more common after perforation. Perforation and abscess formation can also lead to fistula formation in adjacent organs. Perforation rates are consistently >80% in children younger than 5 years of age. Other potential complications include postoperative ileus, diffuse peritonitis portal vein Pyle phlebitis (rare), and adhesive small bowel obstruction. Treatment of the wound infection is opening the wound and healing by secondary intention.

## Chronic Appendicitis

The appendix may be responsible for chronic right lower quadrant pain. The literature describes two seemingly distinct pathologic entities: chronic appendicitis, where the appendix shows histologic signs of chronic inflammation, and appendiceal colic, where a nonobstructing luminal mass (e.g., fecaloma, fibrosis, kink-adhesion, foreign body, parasites, carcinoid, and lymphoid hyperplasia) is found. These diagnoses can only be definitively made following removal of the appendix. These pathologic findings can be found together or in conjunction with acute appendicitis, which further confound the validity of this entity.

Typically, the child will complain of long-standing right lower quadrant pain and may have intermittent tenderness at McBurney's point. Chronic appendicitis and appendiceal colic are diseases of exclusion and will often have normal laboratory values and non-diagnostic imaging.

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# Congenital Hypertrophic Pyloric Stenosis

## PRESENTING COMPLAINTS

A 10-week-old boy was brought with the complaints of:

- Persistent vomiting since 15 days
- Not gaining weight since 15 days

## History of Presenting Complaints

A 10-week-old boy was brought to the pediatric outpatient department with history of persistent vomiting since 15 days and with history of not gaining weight. His mother told that he will vomit immediately if he completes the breastfeeds. According to the mother, child used to vomit all the milk which he had taken. The milk used to come out in curdled form.

## Past History of the Patient

He was the first child of nonconsanguineous marriage. He was delivered at full term with

normal delivery. He cried immediately after delivery. The birth weight was 3 kg. There was no postnatal significant event except for the prolonged physiological jaundice. The child was on breast milk from the beginning. There was no feeding problem in the beginning. He was doing well till the age of 6 weeks. His weight was 4 kg when he had come for immunization. He was normal till the age of 8 weeks. Later he developed vomiting milk which he had taken. His mother had observed a small swelling being present in the upper part of the abdomen after the feed.

## EXAMINATION

Boy was moderately built and nourished. Anthropometric measurements included, the weight was 4.5 kg (40th centile), and the length was 60 cm (70th centile). The head circumference was 39 cm. There were features of mild dehydration. Features of marasmic child were present.

The child was afebrile. The pulse rate was 120 per minute, the respiratory rate was 26 per minute. The blood pressure recorded was 60/40 mm Hg. There was no pallor, no lymphadenopathy and no cyanosis.

Per abdomen examination revealed presence of small mass moving from left to right. This was more evident when the child was examined after feeding. Visible gastric peristalsis (**Fig. 1**) was present. There was no organomegaly. Cardiovascular and respiratory systems were normal.

## INVESTIGATION

Hemoglobin	: 13 g/dL
TLC	: 13,100 cells/cu mm
DLC	: $P_{72} L_{26} M_2$
ESR	: 32 mm in the 1st hour
AEC	: 360 cells/cu mm
Serum electrolytes	: Na—110 mEq/L
	K—5 mEq/L
	Cl—80 mEq/L
X-ray plain erect abdomen	: Thick-walled active stomach

### CASE AT A GLANCE

#### Basic Findings

Length	: 60 cm (70th centile)
Weight	: 4.5 kg (40th centile)
Temperature	: 36.5°C
Pulse rate	: 120 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 60/40 mm Hg

#### Positive Findings

##### History

- Vomiting
- Loss of weight
- Not gaining weight
- Normal at birth

##### Examination

- Signs of dehydration
- Visible gastric peristalsis
- Loss of weight

##### Investigation

- Electrolytes Na: 110 mEq/L
  - K: 5 mEq/L
  - Cl: 80 mEq/L
- X-ray plain
  - Erect abdomen: Thick-walled active stomach



**Fig. 1:** Visible gastric peristalsis.

## DISCUSSION

Boy was normal at birth. He was doing well till the age of 6 weeks. Later he developed persistent vomiting. The presence of visible mass moving from left to right side after the feeding suggests congenital hypertrophic pyloric stenosis.

If affects frequently in the first born male infants. Multifactorial inheritance is likely. Male infants are affected four times more than females. The incidence of this is more with type B and O blood group. The cause of pyloric stenosis is unknown, but many factors have been implicated. Abnormal muscle innervation, maternal stress in the third trimester, administration of prostaglandin E to maintain the patency of the ductus have been implicated as the etiological factors.

Hypertrophic pyloric stenosis (HPS) is a condition of infancy that occurs between 2 and 10 weeks of age, most commonly between 5 and 6 weeks of age. In premature infants, it presents at a later chronological age, but earlier postconceptional age. It is characterized by hypertrophy of the circular muscle of the pylorus causing gastric outlet obstruction.

## PATHOGENESIS

Despite advances in the field, HPS is still considered idiopathic. It appears to result from the interplay of genetic predisposition with local tissue factors, as well as pre- and postnatal environmental exposures.

Hypertrophic pyloric stenosis is not congenital, as it has been shown by studying healthy newborns with ultrasound (US) and upper gastrointestinal (UG) fluoroscopy.

All infants had normal studies after birth, but a few of them went on to develop HPS, while most did not. Pyloric stenosis does not develop without initiation of feeds, so the interaction of feeds and other pre- and postnatal micro- and macroenvironmental factors with the developing pyloric muscle is likely the key element to trigger the condition in genetically predisposed individuals. The majority of hypertrophy happens in the circular muscle layer, which thickens and elongates, but thickening of the mucosa is also present. The natural course of HPS is that of resolution as evidenced by the feasibility of nonoperative treatment with atropine and/or parenteral nutrition.

A diffuse hypertrophy and hyperplasia of the smooth muscle narrows the antrum of the stomach to a fine channel that easily becomes obstructed. The antral region is elongated and thickened to as much as twice its normal size. The muscular thickening is never confined to isolated band or circular muscle fiber called pyloric sphincter. It extends proximally well into the antrum and ends distally quite abruptly where the duodenum begins.

The appearance of the pylorus is that of enlarged, pale muscle mass usually measuring 2–2.5 cm in length and 1–1.5 cm in diameter. Histologically, the mucosa and adnexa are normal. There is marked muscle hypertrophy primary involving circular layer. This produces partial or complete luminal occlusion.

Milk curds produce edema of the pyloric mucosa and submucosa leading to partial luminal obstruction and hypertrophy of pyloric muscle. There is decrease in ganglion cells in the circular muscles in pylorus. Ganglion cells are immature.

A hereditary component of pyloric stenosis is consistent with a multifactorial, sex-modified threshold model of inheritance, in which 5.5% of sons and 2.5% of daughters of an affected father develop HPS.

There is no single gene that is responsible for HPS, but genome-wide analyses have revealed several potential contributing loci including the gene encoding the enzyme neuronal nitric oxide synthase (nNOS), a family of genes encoding transient receptor potential cation channels, and a locus adjacent to the apo-lipoprotein gene cluster.

Complex interactions between nerve and muscle cells and the extracellular matrix of pyloric tissue have been studied along with the influences of hormones, growth factors, and local paracrine mediators. Gastrin and prostaglandin E may be

contributing factors, as well as increased levels of insulin-like growth factor-I, platelet-derived growth factor, epidermal growth factor, and transforming growth factor in pyloric muscle.

The activity of nitric oxide (NO) in hypertrophied pylorus is decreased, resulting in lower levels of NO that mediates relaxation of smooth muscle. The distribution and interaction of extracellular matrix proteins is altered compared to the normal pylorus, and multiple abnormalities in innervation have been described. Interstitial cells of cajal are non-neuronal cells that interact with the enteric nervous system and secrete carbon monoxide and NO, both mediators of smooth muscle relaxation. They are decreased in HPS, possibly contributing to smooth muscle spasm and hypertrophy.

Pyloric stenosis has been associated with eosinophilic gastroenteritis, Apert syndrome, Zellweger syndrome, trisomy 18, Tracheoesophageal fistula, Smith-Lemli-Opitz syndrome, and Cornelia-de-Lange syndrome.

## CLINICAL FEATURES (FIG. 2)

Pyloric stenosis is usually not present at birth and is more concordant in monozygotic than dizygotic twins. It has slight association with hiatus hernia and esophageal atresia. High levels of serum gastrin may be found. Gastrin levels are elevated neurotransmitter substance which produces chronic pylorospasm leading to muscle hypertrophy. Vasoactive intestinal polypeptide (VIP) and deficiency of nitric oxide in pyloric

muscle resulting in failed relaxation. Premature infants with hypertrophic pyloric stenosis present 2 weeks later than term infants.

Forceful (projectile) nonbilious emesis after feeds is the hallmark of HPS. It develops progressively, increasing in frequency and force. Infants are of a typical age group (2–8 weeks) and otherwise well. They are hungry and want to eat again immediately after emesis. Weight loss and dehydration develop in more advanced cases. Hematemesis may be present if there is concomitant gastritis. Due to dehydration and loss of gastric acid, the typical metabolic finding is hypokalemic, hypochloremic metabolic alkalosis.

Initially, there is only regurgitation and occasionally non-projectile. Vomiting becomes projectile usually within 1 week after the onset. It generally occurs during or shortly after the feeding but some time, it occurs several hours later.

Nonbilious vomiting is the initial symptom of pyloric stenosis. The vomiting may or may not be projectile initially but is usually progressive, occurring immediately after a feeding. Emesis might follow each feeding, or it may be intermittent. The vomiting usually starts after 3 weeks of age, but symptoms can develop as early as the 1st week of life and as late as the 5th month.

In some instances, vomiting occurs after feeding. The vomiting contains only gastric content. But sometimes may be blood stained. Approximately, 20% have intermittent emesis from birth that then progresses to the classic picture. After vomiting, the infant is hungry and wants to feed again. As vomiting continues, a progressive loss of fluid, hydrogen ion, and chloride leads to critical deficits of potassium and sodium and hypochloremic metabolic alkalosis. There is striking decrease in chloride concentration and increase in pH and carbon dioxide content. This leads to hypochloremic alkalosis. Correction of these chemical changes requires replacement of sodium chloride and potassium. Intravenous administration of 5% Dextrose in isotonic sodium chloride to which potassium chloride is added is recommended. Serum potassium levels are usually maintained, but there may be a total body potassium deficit.

Hyperbilirubinemia is the most common clinical association of pyloric stenosis, also known as icteropyloric syndrome. Unconjugated hyperbilirubinemia is more common than conjugated and usually resolves with surgical correction. It may be associated with a decreased level of glucuronosyltransferase as seen in approximately

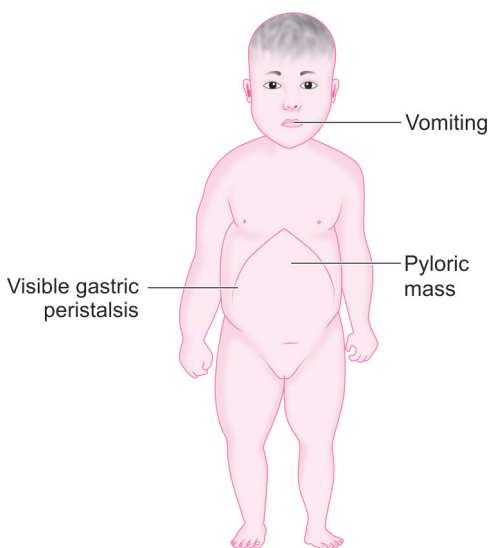


Fig. 2: Clinical features.

5% of affected infants; mutations in the bilirubin uridine diphosphate glucuronosyltransferase gene (UGT1A1) have also been implicated. Other coexistent clinical diagnoses have been described, including eosinophilic gastroenteritis, hiatal hernia, peptic ulcer, congenital nephrotic syndrome, congenital heart disease, and hypothyroidism.

The diagnosis has traditionally been established by palpating the pyloric mass. The mass is firm, movable, approximately 2–2.5 cm in length, hard, best palpated from the left side, and located above and to the right of the umbilicus in the mid-epigastrium beneath the liver's edge. The olive is easiest palpated after an episode of vomiting. After feeding, there may be a visible gastric peristaltic wave that progresses across the abdomen.

#### ESSENTIAL DIAGNOSTIC POINTS

- First born male infants.
- Multifactorial inheritance is likely.
- A diffuse hypertrophy and hyperplasia of the smooth muscle narrows the antrum.
- Abnormal muscle innervation, maternal stress in the third trimester.
- Administration of prostaglandin E to maintain the patency of the ductus have been implicated as the etiological factors.
- Decrease in ganglion cells in the circular muscles in pylorus.
- Projectile vomiting, VGP, FTT, jaundice.

On examination, visible peristalsis preceding from left upper quadrant towards pylorus in right upper quadrant of abdomen is more prominent after feeds, before vomiting. Diagnosis is mainly clinical confirmation by palpating the mass. This is only feasible in a comfortable and relaxed infant with a decompressed stomach, which takes time, patience, and experience. Hyperperistaltic waves in the dilated stomach may be appreciated through the abdominal wall in the left upper quadrant.

Physical examination reveals varying degree of dehydration and lethargy depending on the metabolic state. Weight loss may occur. Decreased elasticity of the skin and loss of subcutaneous tissue may occur. Eyes may be sunken and fat pads of cheeks may be lost giving old man's appearance.

In more advanced cases, oliguria, decreased skin turgor, lethargy, and delayed capillary refill may be present due to dehydration, and the infant may appear emaciated. Jaundice is present in up to 5% of infants presenting with HPS. This is thought to reflect a decrease in hepatic glucuronosyltransferase activity associated with starvation, or may reflect an early manifestation of Gilbert syndrome.

#### GENERAL FEATURES

- Nonbilious vomiting
- Projectile vomiting
- Prolonged physiological jaundice
- Failure to gain weight

#### INVESTIGATION

Two imaging studies are commonly used to establish the diagnosis. Ultrasound examination confirms the diagnosis in the majority of cases. Criteria for diagnosis include pyloric thickness 3–4 mm, an overall pyloric length 15–19 mm and pyloric diameter of 10–14 mm. Ultrasonography has a sensitivity of approximately 95%.

Ultrasonographic examination may be done in suspected patients. Serum sodium, potassium and bicarbonate levels suggest hypokalemic alkalosis which supports the diagnosis.

#### Infantile Form

Plain X-ray abdomen shows dilated stomach.

#### Barium Study

- Elongation and narrowing of pyloric canal (2–4 cm in length)
- Double or triple-track sign—crowding of mucosal folds in pyloric channel
- String sign—passing small barium streak through pyloric channel—double tract sign
- Twinning recess—diamond sign—transient triangular tent-like cleft/niche in mid portion of pyloric canal with the apex pointing inferiorly secondary to mucosal bulging between two separated hypertrophied muscle bundles on greater curvature side within pyloric canal.
- Out pounding along lesser curvature due to disruption of antral peristalsis.
- Mushroom sign—Kirklin sign—indentation of base of bulb.
- Caterpillar sign—hypertrophied walls.

#### Ultrasonography Findings

- *Target sign:* Hypoechoic ring of hypertrophied pyloric muscle around Echogenic mucosa centrally on cross-section.
- *Cervic sign:* Indentation of muscle mass on fluid-filled antrum on longitudinal section
- Pyloric wall thickness more than 4 mm
- Pyloric muscle wall thickness more than 14 mm
- Elongated pyloric canal more than 17 mm in length



- Exaggerated peristaltic waves
- Delayed gastric emptying of fluid into duodenum

#### LABORATORY SALIENT FINDINGS

- Ultrasonographic examination
- Serum sodium, potassium and bicarbonate levels suggest hypokalemic alkalosis
- Barium study

### DIFFERENTIAL DIAGNOSIS

Gastroesophageal reflux, with or without a hiatal hernia, may be confused with pyloric stenosis.

Gastroesophageal reflux disease can be differentiated from pyloric stenosis by radiographic studies.

Adrenal insufficiency from the adrenogenital syndrome can simulate pyloric stenosis, but the absence of a metabolic acidosis and elevated serum potassium and urinary sodium concentrations of adrenal insufficiency aid in differentiation.

Inborn errors of metabolism can produce recurrent emesis with alkalosis (urea cycle) or acidosis (organic acidemia) and lethargy, coma, or seizures. Vomiting with diarrhea suggests gastroenteritis, but patients with pyloric stenosis occasionally have diarrhea.

- Gastroesophageal reflux
- Hiatal hernia
- Adrenal insufficiency
- Pyloric duplication
- Duodenal stenosis

### TREATMENT

Hypertrophic pyloric stenosis is not a surgical emergency. Once the diagnosis of HPS is established, the priority is restoration of intravascular volume and electrolyte and acid-base homeostasis. The infant is kept nil per os (NPO), but gastric decompression is avoided to prevent worsening fluid, acid, and electrolyte losses. Resuscitation is initiated with a normal saline bolus of 20 mL/kg, followed by one or more boluses, depending on the level of dehydration, with an end-point of establishing normal urine output. Intravenous (IV) fluids are administered at a rate of 1.5 times maintenance, with 5% dextrose, 0.45% saline, and with 20 mEq/L of potassium chloride to replace potassium lost in emesis and urine. Serum electrolytes are rechecked every 6 to 12 hours and IV fluids adjusted as needed. Once serum bicarbonate and potassium are normalized, which is within 24 hours for most infants,

the patient is safe to have general anesthesia. A single dose of preoperative cefazolin decreases the rate of postoperative wound infection.

Dehydration and dys-electrolytemia should be corrected rapidly. Potassium is added when renal function is restored. The stomach is washed with isotonic saline.

Extramucosal pyloromyotomy remains the standard operation. Treatment of choice is Ramstedt pyloromyotomy. At operation, or after the operation, the stomach is emptied by catheter. The procedure is performed through a short transverse skin incision. The underlying pyloric mass is cut longitudinally to the layer of the submucosa, and the incision is closed. Seromuscular layer of gastric antrum and pylorus is incised. The muscle is split with blunt instrument allowing mucosa to bulge between split muscles. Laparoscopic technique is equally successful. Postoperative vomiting occurs in half the infants and is thought to be secondary to edema of the pylorus at the incision site. In most infants, however, feedings can be initiated within 12–24 hours after surgery and advanced to maintenance oral feedings within 36–48 hours after surgery. Persistent vomiting suggests an incomplete pyloromyotomy, gastritis, gastroesophageal reflux disease, or another cause of the obstruction. The surgical treatment of pyloric stenosis is curative, with an operative mortality of 0–0.5%.

Oral feeding is started after 4–6 hours. About 4 mL of 5% dextrose in saline solution is given hourly for 4–5 hours. Then once in 4 hours schedule is started. Persistence of vomiting beyond 5th postoperative day suggests incomplete pyloromyotomy or associated hiatus hernia or achalasia or gastritis.

Endoscopic balloon dilation has been successful in infants with persistent vomiting secondary to incomplete pyloromyotomy.

Conservative management with nasoduodenal feedings is advisable in patients who are not good surgical candidates. Oral and intravenous atropine sulfate (pyloric muscle relaxant) has also been described when surgical treatment is not available. In conservative protocols, atropine is administered intravenously at a dose of 0.01 mg/kg 6 times a day 5 minutes before feeding. During atropine infusion, the heart rate needs to be continuously monitored by electrocardiography. Oral feeding is started at a volume of 10 mL of formula feeds 6 times a day. The volume is increased day-by-day until patients tolerate 150 mL/kg/day unless vomiting occurs more than twice a day.



When patients are able to tolerate the full volume of formula without vomiting more than twice a day, 0.02 mg/kg atropine is administered orally 6 times a day before feeding.

Fluid therapy should be continued until the infant is rehydrated and serum bicarbonate concentration is less than 30 mEq/L. This tells the correction of alkalosis. Correction of alkalosis is necessary to prevent postoperative apnea.

## COMPLICATIONS

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- Incomplete pyloromyotomy
- Perforation

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# Diaphragmatic Hernia

## PRESENTING COMPLAINTS

A 2-day-old male boy was brought with the complaints of:

- Excessive crying since birth
- Irritable since 6 hours
- Restless since 4 hours
- Breathlessness since 2 hours

## History of Presenting Complaints

A 2-day-old male baby was brought to the hospital with severe respiratory distress. The mother was complaining that child was irritable, restless and crying. Child had respiratory distress. It was evident with the marked subcostal recession with the indrawing of the abdomen. Mother also complained that the child was not taking feeds and it was vomiting and not sucking at the breast. The mother told that she had noticed bluish color of the lips and extremities.

## Past History of the Patient

This boy was the second sibling of the consanguineous marriage. The child was born at term

with normal vaginal delivery. He cried immediately after the delivery. He was taking feeds. There was mild respiratory distress. The resident doctor examined and developed doubt about position of the heart towards the right. Later he advised to take child to higher institute for management.

## EXAMINATION

On examination, child was restless and irritable. It never used to be comfortable on lying down. He was restless. Features of intrauterine growth retardation (IUGR) were present. Anthropometric measurements included the length 51 cm (75th centile), the weight 3 kg (50th centile), and head circumference was 35 cm.

The child was afebrile, the heart rate was 146 per minute. The respiratory rate was 62 per minute. Blood pressure was 50/40 mm Hg. Cyanosis was present. There was no pallor and no icterus. There was no edema. There was marked subcostal recession.

Per abdomen examination revealed scaphoid abdomen. The normal physiological hepatomegaly was present on right side below the costal margin. Cardiovascular examination revealed that heart sounds were better heard at the right side. Chest auscultation revealed the presence of bowel sounds on the left side.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 9,800 cells/cu mm
DLC	: $P_{75} L_{20} E_3 M_2$
CRP	: 2000 mg/L (Normal 67–1800 mg/L)
X-ray chest	: Shifting of mediastinum on the right side. Free and air-filled loop in the left chest

## DISCUSSION

A diaphragmatic hernia is defined as a communication between the abdominal and thoracic cavities with or without abdominal contents in the thorax. The etiology is usually congenital but

### CASE AT A GLANCE

#### Basic Findings

Length	: 51 cm (75th centile)
Weight	: 3 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 146 per minute
Respiratory rate	: 62 per minute
Blood pressure	: 50/40 mm Hg

#### Positive Findings

##### History

- Respiratory distress
- Cyanosis
- Feeding difficulties

##### Examination

- Tachypnea
- Scaphoid abdomen
- Shifting of the mediastinum

##### Investigation

- X-ray chest—shifting of mediastinum on the right side
- Fluid and air-filled loop in the left chest

may be traumatic. The symptoms and prognosis depend on the location of the defect and associated anomalies.

The incidence of congenital diaphragmatic hernia (CDH) is between 1/2,000 and 1/5,000 live births with females affected twice as often as males. Defects are more common on the left (85%) and are occasionally (<5%) bilateral, pulmonary hypoplasia and malrotation of the intestine are part of the lesion. Associated anomalies include central nervous system (CNS) lesions, esophageal atresia, omphalocele, and cardiovascular lesions. CDH is recognized as part of chromosomal syndromes: trisomy 21, trisomy 13, trisomy 18, Brachmann-de Lange, Pallister-Killian, and Turner.

It is the congenital herniation of the abdominal contents into the thoracic cavity (**Fig. 1**). Symptomatology and prognosis depends upon location of the defect and associated anomalies. The defect may be at the esophageal hiatus (hiatal), paraesophageal (adjacent to the hiatus), retrosternal (Morgagni), or at the posterolateral (Bochdalek) portion of the diaphragm.

The term CDH typically refers to the Bochdalek form. These lesions may cause significant respiratory distress at birth, can be associated with other congenital anomalies, and have significant mortality and long-term morbidity. The size of the defect is variable ranging from a small hole to complete agenesis of this area of the diaphragm. This may be associated with anomalies of the other organ system.



**Fig. 1:** Loops of bowel left chest.

## TYPES OF DIAPHRAGMATIC HERNIA

The most common type of CDH, a Bochdalek hernia, occurs through a posterior defect in the diaphragm. Defects in the central and lateral portions of the diaphragm result in a less common anterior retrosternal hernia, a Morgagni hernia. Often, the stomach, spleen, and most of the intestines herniate into the thorax.

Herniation of the, abdominal contents interferes with lung development and growth, and the resulting lung compression results in pulmonary hypoplasia that is most severe on the ipsilateral side, although both lungs may be affected. There is a marked reduction in the number of bronchi and alveoli associated with a decrease in cross-sectional area of the pulmonary vasculature.

In addition to parenchymal maldevelopment, the intra-acinar pulmonary arteries have increased muscularization. Pulmonary capillary blood flow is decreased because of the small cross-sectional area of the pulmonary vascular bed, and flow may be further decreased by abnormal pulmonary vasoconstriction. Surfactant production may also be affected by pulmonary hypoplasia in infants with CDH.

## PRENATAL DIAGNOSIS

Diaphragmatic hernia is often diagnosed by fetal ultrasound, which can reveal abdominal organs and fluid-filled bowel with peristalsis in the thorax, and a shift of the heart and mediastinum away from the side of the hernia. Polyhydramnios, pleural effusions, and ascites often are present. The differential diagnosis of these sonographic findings includes congenital cystic adenomatoid malformation, bronchogenic cysts, cystic teratoma, and neurogenic tumors. If CDH is suspected, fetal echocardiography and karyotype should be performed for potential prenatal diagnosis of common associated malformations. The patient should be referred to a quaternary treatment center for prenatal counseling and delivery.

## PATHOLOGY AND ETIOLOGY

Separation of developing thoracic and abdominal cavities is accompanied by closure of posterolateral pleuroperitoneal canals. This occurs in the 8th week of gestation.

Failure of this canal to close is responsible for the defect. The defect may be small and sac-like or include entire diaphragm. Both the lungs are small but lungs on side of the defect may be severely affected. When little or no respiratory distress occurs the hernia may not be detected until infancy and childhood.

There will be partial herniation of the stomach through the esophageal hiatus. Unrecognized diaphragmatic hernia has been the cause of sudden deaths in infants and toddlers. There will be phrenic nerve paralysis with displacement of abdominal contents upwards.

Failure of the development of posterolateral portion of the diaphragm results in persistence of pleuroperitoneal canal or foramen of Bochdalek. This allows the viscera to occupy chest cavity, abdomen underdeveloped and scaphoid.

Developing lung buds project into the pericardioperitoneal cavities to form pleural cavities and the membranes fuse with dorsal mesentery of developing foregut medially and septum transversum ventrally. Closure of pleuroperitoneal membrane is assisted by the myoblasts.

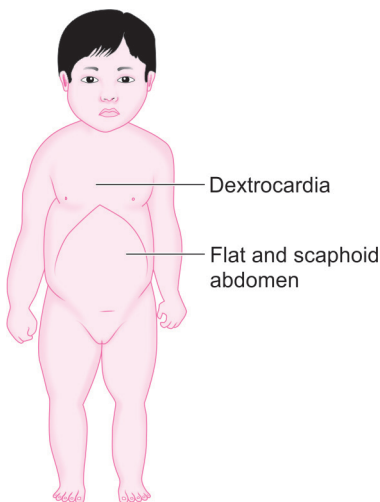
Eventration is the upward displacement of abdominal contents into an outpouching or sac-like structure of the diaphragm.

Pulmonary hypoplasia is characterized by a reduction in pulmonary mass and the number of bronchial divisions, respiratory bronchioles and alveoli. The pathology of pulmonary hypoplasia and CDH includes abnormal septa in the terminal sacculi, thickened alveoli, and thickened pulmonary arterioles.

## CLINICAL FEATURES (FIG. 2)

Clinical presentation of CDH depends on the type and size of the hernia. Infants with a large left-sided hernia may present with a scaphoid abdomen and significant respiratory symptoms in the delivery room.

Majority of the infants will have severe respiratory distress within 1 hour after the delivery.



**Fig. 2:** Clinical features.

Child with delayed presentation may experience vomiting as a result of intestinal obstruction or mild respiratory symptoms. Rarely incarceration of the intestine produce an ischemia with sepsis and cardiorespiratory collapse.

After delivery, a chest radiograph is needed to confirm the diagnosis. In some with an Echogenic chest mass, further imaging is required. The differential diagnosis may include other diaphragm disorders such as eventration, a cystic lung lesion (pulmonary sequestration, cystadenomastoid malformation), and others.

Respiratory distress is a cardinal sign in babies with CDH. It may occur immediately after birth or there may be a “honeymoon” period of up to 48 hours during which the baby is relatively stable. Early respiratory distress, within 6 hours after birth, is thought to be a poor prognostic sign. Respiratory distress is characterized clinically by tachypnea, grunting, use of accessory muscles, and cyanosis. Children with CDH may also have a scaphoid abdomen and increased chest wall diameter.

Bowel sounds may also be heard in the chest with decreased breath sounds bilaterally. The point of maximal cardiac impulse may be displaced away from the side of the hernia if mediastinal shift has occurred. A chest X-ray and passage of a nasal gastric tube are all that is usually required to confirm the diagnosis.

Approximately 40% of infants with CDH have associated anomalies, most with minimal effect on survival, and others that significantly affect survival, including chromosomal and complex cardiac defects. During fetal life, the left ventricle is often small (probably as a result of increased intrathoracic pressure) and left ventricular output is reduced. Postnatally, the left ventricular size and output may improve with correction of the hernia.

Congenital diaphragmatic hernia can be diagnosed on prenatal ultrasonography (between 16 and 24 weeks of gestation) in >50% of cases. High-speed fetal MRI can define the lesion. Findings on ultrasonography may include polyhydramnios, chest mass, mediastinal shift, gastric bubble or a liver in thoracic cavity, and fetal hydrops.

## Associated Anomalies

- Malrotation
- Patent ductus arteriosus
- Ventricular septal defect
- Coarctation
- Undescended testes
- Renal anomalies
- Duodenal atresia

- Meckel's diverticulum
- Hirschsprung's disease

Pulmonary hypoplasia leads to barotrauma, alveolar rupture, emphysema pneumomediastinum and pneumothorax—surgical emphysema

Antenatal features include polyhydramnios, mediastinal displacement and absence of intra-abdominal stomach bubble.

#### ESSENTIAL DIAGNOSTIC POINTS

- Congenital herniation of the abdominal contents into the thoracic cavity
- Severe respiratory distress within 1 hour after the delivery includes dyspnea and cyanosis
- The lung of the affected side is compressed and often hypoplastic
- Abdomen is usually small and scaphoid is contour
- If the respiratory embarrassment is not released, shock and hypoxia occur

In severe causes, stomach and large part of the intestine will displace the lungs and heart. The lung of the affected side are compressed and often hypoplastic. There will be decreased number of airways and blood vessels and diminished lung volume. Severe respiratory distress includes dyspnea and cyanosis since birth.

The physical finding depends upon the degree of displacement in the newborn infant. Abdomen is usually small and scaphoid is contour. The infant is cyanotic and has respiratory retraction. If the respiratory embarrassment is not released, shock and hypoxia occur.

Gastroesophageal reflux disease is reported in more than 50% of children with CDH. It is more common in those children whose diaphragmatic defect involves the esophageal hiatus. Recurrent diaphragmatic hernia is reported in 5–20% in most series. Children with patch repairs are at highest risk.

Children with CDH typically have delayed growth in the first 2 years of life. Contributing factors include poor intake, gastroesophageal reflux disease energy.

#### GENERAL FEATURES

- Mediastinal shift
- Grunting
- Cyanosis
- Respiratory distress

### DIAGNOSIS

Chest radiograph is usually diagnostic. The lateral view frequently demonstrates the intestine passing through the posterior portion of the diaphragm. Chest X-ray shows gas-filled bowel

loops, displacement of lung, herniated liver or spleen ipsilateral pneumothorax.

Ultrasonography and fluoroscopy are helpful in distinguishing eventration from the true hernia. Computed tomography may be necessary to exclude pneumatocele or complicated effusion.

The prenatal diagnosis of CDH can be made by using fetal sonography as early as 15 weeks of gestation. Sonographic findings include herniated abdominal viscera, abnormal anatomy of the upper abdomen and mediastinal shift away from the herniated viscera. The high-risk fetus is identified by diagnosis early in gestation, a dilated stomach in the chest, low lung to thorax ratio, low lung to head ratio and polyhydramnios.

#### LABORATORY SALIENT FINDINGS

- *Chest radiograph:* Lateral view frequently demonstrates the intestine passing through the posterior portion of the diaphragm.
- Chest X-ray shows gas-filled bowel loops, displacement of lung, herniated liver or spleen ipsilateral pneumothorax.
- Ultrasonography and fluoroscopy are helpful in distinguishing eventration from the true hernia.
- Computed tomography may be necessary to exclude pneumatocele or complicated effusion.

### COMPLICATIONS

Complications include abnormalities in the lung function. There is significant decrease in vital capacity and peak expiratory flow, decreased lung compliance and tidal volume. Survivors will have restrictive lung disease and respiratory failure. Developmental delay, abnormal hearing or vision may occur. Seizure is a neurological complication. Pectus excavatum, scoliosis and recurrent hernia are long-term complications.

### DIFFERENTIAL DIAGNOSIS

- Congenital pneumonia
- Aspiration pneumonitis
- Transient tachypnea of the newborn
- Hyaline membrane disease

### TREATMENT

Currently, the preferred management strategy for CDH is medical stabilization with appropriate cardiorespiratory support, including high-frequency oscillatory ventilation, nitric oxide (NO), or extracorporeal membrane oxygenation (ECMO) for several days to allow for physiologic stabilization and improvement in pulmonary hypertension. The surgical approach is through a subcostal

opening with primary repair if enough diaphragm tissue is available. For those with a more significant defect, closure with a patch may be required. The use of chest drains or tubes postoperatively has also decreased in the past few years, but a consensus on their use has not been reached.

## Initial Management

Initial resuscitation consists of stabilization with sedation and paralysis and modest hyperventilation, i.e., the partial pressure of the carbon dioxide of 25–30 mm Hg. Volume resuscitation, dopamine and bicarbonate are useful. If the infant stabilizes and demonstrates stable pulmonary vascular resistance without significant right to left shunt, repair of the diaphragm is performed in 24–72 hours.

Aggressive respiratory support is often needed in children with CDH. This includes rapid endotracheal intubation, sedation, and possibly paralysis. Arterial (preductal and postductal) and central venous (umbilical) lines are mandated, as are a urinary catheter and nasogastric tube. A preductal arterial oxygen saturation ( $\text{SpO}_2$ ) value 85% could be the minimum goal.

Gentle ventilation with permissive hypercapnia reduces lung injury, need for ECMO, and mortality. Factors that contribute to pulmonary hypertension (hypoxia, acidosis, hypothermia) should be avoided. Echocardiography is important to guide therapeutic decisions by measuring pulmonary and system vascular pressures and defining the presence of cardiac dysfunction. Routine use of inotropes is indicated in the presence of left ventricular dysfunction. Babies with CDH may be surfactant deficient. Although surfactant is commonly used, no study has proven that it is beneficial in treatment CDH.

## Ventilation Strategies

Conventional mechanical ventilation, high-frequency oscillatory ventilation (HFOV), and ECMO are the three main strategies to support respiratory failure in the newborn with CDH. The goal is to maintain oxygenation and carbon dioxide elimination without inducing volutrauma. The first modality to be used is conventional ventilation. Hyperventilation to induce alkalosis and decrease ductal shunting has not proved effective and should be avoided. Permissive hypercapnia has reduced lung injury and mortality rates in several studies. HFOV can be used early to prevent lung injury by using lower airway pressures.

Pulmonary hypoplasia and pulmonary hypertension are significant contributors to mortality in CDH. Pulmonary hypertension has a reactive component, due to the changing resistance of the pulmonary arterioles, and a fixed component due to the diminished cross-sectional area of the pulmonary vascular bed. Mechanical ventilation should aim to maintain appropriate lung volumes and adequate oxygenation while minimizing lung injury. Many centers prefer to use high-frequency ventilation, especially high-frequency oscillatory ventilation, before on and alkalosis in CDH has been replaced before and after surgery.

## Extracorporeal Membrane Oxygenation

If stabilization is not possible most infants require ECMO support. Extracorporeal membrane oxygenation with paralysis and nasogastric suction may produce dramatic reduction of the volume of the herniated viscera. Surfactant administration has also been shown to produce transient improvement.

The availability of ECMO and the utility of preoperative stabilization have improved survival of babies with CDH. ECMO is the therapeutic option in children in whom conventional ventilation or conventional ventilation and HFOV fail. ECMO is most commonly used before repair of the defect.

Birth weight and the 5-minute Apgar score may be the best predictors of outcome in patients treated with ECMO. The lower limit of weight for ECMO is 2,000 g.

The duration of ECMO for neonates with diaphragmatic hernia is longer (7–14 days) than for those with persistent fetal circulation or meconium aspiration, and may last up to 2–4 weeks. Timing of repair of the diaphragm while the infant receives ECMO is controversial. The recurrence of pulmonary hypertension is associated with a high mortality, and weaning from ECMO support should be cautious. If the patient cannot be weaned from ECMO after repair of CDH, options include discontinuing support and, in rare cases, lung transplantation.

## Surgical Repair

Prompt and aggressive, preoperative care is essential. This generally includes mechanical ventilation with 100% oxygen, sedation with narcotics, muscle paralyses, controlled alkalosis with hyperventilation, intravenous sodium bicarbonate and vasopressors.

The ideal time to repair the diaphragmatic defect is under debate. Most experts wait at least



48 hours after stabilization and resolution of the pulmonary hypertension. Good relative indicators of stability are the requirement for conventional ventilation only, a low peak inspiratory pressure, and a  $\text{FiO}_2 < 50$ . If the newborn is on ECMO, an ability to be weaned from this support should be a consideration before surgical repair. In some centers, the repair is done with the cannulas in place; in other centers, the cannulas are removed.

The abdominal surgical repair approach is favored. The accompanied malrotation should be managed. Abdominal wall may be left open with skin only closed. A subcostal approach is the most frequently used. This allows for good visualization of the defect and, if the abdominal cavity cannot accommodate the herniated contents, a polymeric silicone (silastic) patch can be placed. Both laparoscopic and thoracoscopic repairs have been reported, but these should be reserved for only the most stable infants.

Surgical repair of the diaphragmatic defect should be performed during the neonatal period. The exact timing of surgery depends on a number of variables, but over the past two decades, practice has changed. In the past, surgical intervention was considered emergent, and as a consequence, postoperative management was characterized by severe pulmonary hypertension and tension pneumothoraces, resulting in poor outcomes.

## Vasodilator Therapy

### Nitric Oxide

Although NO is an effective treatment for infants with PPHN in general, it has not had the same success for infants with CDH, and may actually increase the death rate. Nonetheless, it is still widely used in the management of CDH.

Nitric oxide is a selective pulmonary vasodilator. Its use reduces ductal shunting and pulmonary pressures and results in improved oxygenation. Although it has been helpful in PPHN, randomized trials have not demonstrated improved survival or reduced need for ECMO when NO is used in newborns with CDH.

Tolazoline reduces pulmonary vascular resistance.

*Thromboxane inhibitors:* 5–20 mg/kg/min. Nitroprusside/nitroglycerine/phenoxybenzomine.

## New Modalities

New modalities include surfactant replacement therapy, liquid ventilation, intratracheal pulmonary

ventilation and pulmonary lobe transplantation. Prenatal repair of the diaphragmatic hernia is abandoned as there was no improvement in survival or morbidity in randomized trial.

Current prenatal therapy of CDH is directed including trachea, which results in enlargement of lungs with retained fluid. The baby is then delivered by planned cesarean section, at which time trachea is repaired or intubated, with the baby remaining in placental support.

Fetal surgery includes nitric oxide gas inhalation, intrauterine repair of diaphragmatic hernia.

## PROGNOSIS

The incidence of spontaneous fetal demise is 7–10%. Relative predictors of a poor prognosis include an associated major anomaly, symptoms before 24 hours of age, severe pulmonary hypoplasia, herniation to the contralateral lung, and the need for ECMO. Pulmonary problems continue to be a source of morbidity for long-term survivors of CDH.

Neurocognitive defects are common and may result from the disease or the interventions. The abnormalities with ECMO for other diagnoses include transient and permanent developmental delay, abnormal hearing or vision, and seizures. Serious hearing loss may occur in children who under ECMO.

Other long-term problems occurring in this population is pectus excavatum and scoliosis.

Regardless of mode of therapy, the goal is to reverse the baby's persistent pulmonary hypertension, with right to left shunting of oxygen, poor blood across the open foramen ovale and ductus arteriosus.

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# Duodenal Atresia

## PRESENTING COMPLAINTS

A 2-day-old boy was brought with the complaints of:

- Persistent vomiting since birth
- Mild distension of abdomen

## History of Presenting Complaints

A 2-day-old boy was found in the postnatal ward with history of persistent vomiting. His mother told that in the beginning her child was vomiting the breast milk which he was taking. Later mother noticed the greenish colored vomitus. Vomiting used to be non-projectile type. Mother had also noticed mild distension of abdomen. For complaints of vomiting and mild distension, sister in-charge of the ward had given stomach wash. The color of the stomach aspirate was greenish and the amount was more than 30 mL.

## Past History of the Patient

This boy was the only sibling of consanguineous marriage. Baby was born at term with normal delivery. He cried immediately after the delivery. Birth weight was 2.8 kg. He started taking the feeds immediately after delivery. Child was vomiting

after taking feeds, but resident doctor assured her considering it as normal with every newborn in the beginning. Mother gave the history of doubtful hydramnios antenatally.

## EXAMINATION

On examination, the child moderately built and nourished. He was just lying on the bed. The activity of the child was not satisfactory. Anthropometric measurement included the length was 50 cm (50th centile), the weight was 2.75 kg (25th centile), and the head circumference was 34 cm.

Boy was afebrile. The heart rate was 120 per minute and the respiratory rate was 38 per minute. The blood pressure recorded was 60/50 mm Hg. There was no pallor, no icterus, no lymphadenopathy and no cyanosis.

Per abdomen examination revealed mild distension in the upper abdomen. No visible gastric peristalsis. Bowel sounds were sluggish. Respiratory system revealed presence of crepitations at the basal regions. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 7,600 cells/cu mm
DLC	: $P_{80} L_{18} E_2 M_0$
Serum electrolytes	: Na—110 mEq/L K—4 mEq/L Cl—98 mEq/L
X-ray erect abdomen	: Double-bubble, appearance of gas and fluid filled levels in stomach and duodenum

## DISCUSSION

Congenital duodenal obstruction caused by atresia is an intrinsic defect of bowel formation. Duodenal atresia is limited to the first and second parts of the duodenum. About 85% of cases are distal to the entry of the bile duct into the duodenum. The most common site is at ampulla. It can also result from

### CASE AT A GLANCE

#### Basic Findings

Length	: 50 cm (50th centile)
Weight	: 2.75 kg (25th centile)
Temperature	: 37°C
Pulse rate	: 120 per minute
Respiratory rate	: 38 per minute
Blood pressure	: 60/50 mm Hg

#### Positive Findings

##### History

- Vomiting
- Bile-stained vomitus
- More than 30 mL of gastric aspirate
- Polyhydramnios

##### Examination

- Mild upper abdominal distension

##### Investigation

- X-ray abdomen: Double-bubble appearance

extrinsic compression by abnormal neighboring structures (e.g., annular pancreas, preduodenal portal vein) duplication cysts, or congenital bands associated with malrotation. Although intrinsic and extrinsic causes of duodenal obstruction occur independently, they can also coexist.

Duodenal atresia complicates 1 per 10,000 live births and accounts 25–40% of all intestinal atresias. Duodenal atresia results from failed recanalization of the intestinal lumen during gestation.

Duodenal atresia is thought to arise from delayed vacuolization of the embryonic intestinal lumen. This accounts both for the mucosal diaphragm within the duodenum and for duodenal atresia. Throughout the 4th and 5th week of normal fetal development, the duodenal mucosa exhibits rapid proliferation of epithelial cells. Persistence of these cells, which should degenerate after the 7th week of gestation leads to occlusion of the lumen (atresia) in approximately two-thirds of cases and narrowing (stenosis) in the remaining one-third.

Duodenal atresia may take several forms: the intact membrane obstructing the lumen, a short fibrous cord connecting the two blind duodenal pouches, or a gap between the nonconnecting ends of the duodenum. The membranous form of atresia is the most common. This causes the obstruction occurring distal to the ampulla of Vater.

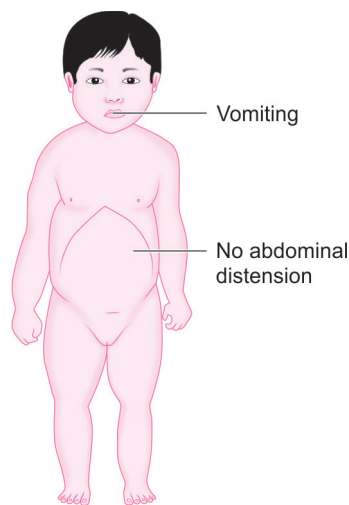
Approximately 50% of infants with duodenal atresia are premature. It is associated with Down syndrome, malrotation, esophageal atresia, congenital heart disease, anorectal and rectal anomalies. It may occur as a result of extrinsic obstruction such as annular pancreas or bands of Ladd.

**Tandler's theory:** Failure of recanalization of duodenal lumen produces stenosis, atresia, formation of a mucosal web. The error occurs most often at the site of papilla of Vater. It is usually associated with annular pancreas, anomalies of intestinal rotation and fixation, biliary and pancreatic anomalies, duodenal obstruction, Down syndrome, malrotation and congenital heart defects.

Duodenum gets greatly dilated with hypertrophied walls with the dilatation of pylorus and stomach. Distal duodenum becomes small and thin walled.

## CLINICAL FEATURES (FIG. 1)

The hallmark of the duodenal obstruction is bilious vomiting, without abdominal distension. This is usually noted on 1st day of life. History of polyhydramnios may be present. This is caused by failure of absorption of amniotic fluid in distal intestine. This fluid may be bile stained because of



**Fig. 1:** Clinical features.

intrauterine vomiting. Jaundice is present in one-third of infant with prolonged vomiting, electrolyte imbalance occurs.

### ESSENTIAL DIAGNOSTIC POINTS

- Bilious vomiting, without abdominal distension noted on 1st day of life
- History of polyhydramnios
- Jaundice is present in infant with prolonged vomiting, electrolyte imbalance occurs
- The most common site being at ampulla
- Failure of recanalization of duodenal lumen produces stenosis, atresia, formation of a mucosal web

## DIAGNOSIS

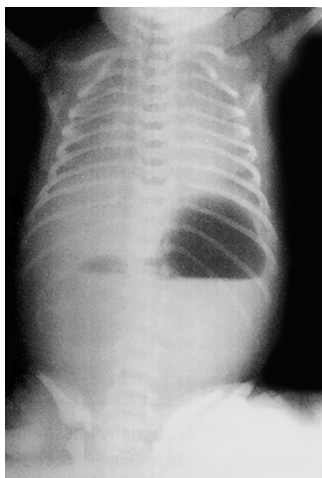
Prenatal ultrasonography (USG) shows dilated, fluid-filled stomach and duodenum. Prompt amniocentesis for karyotype study is essential. Bile stained vomiting within few hours of birth, fullness in epigastrium, rest of the abdomen is scaphoid.

### LABORATORY SALIENT FINDINGS

- Prenatal USG shows dilated, fluid-filled stomach and duodenum
- *X-ray abdomen:* A large, air distended stomach with fluid level, markedly distended first portion of duodenum with a fluid level
- Ultrasonography
- CT scan
- Upper gastrointestinal (GI) contrast study
- Fiberoptic endoscopy

## X-ray Abdomen

A large, air distended stomach with fluid level, markedly distended first portion of duodenum with a fluid level (**Fig. 2**). No evidence of air in the remaining gastrointestinal tract—double bubble sign.



**Fig. 2:** X-ray of duodenal atresia.

In complete atresia, barium enema is done to determine if the malrotation is present or not.

### Ultrasonography

- May show associated annular pancreas
- May show whirlpool sign—characteristic of volvulus
- *Antenatal findings:*
  - Double bubble sign
  - Increased gastric peristalsis
  - Polyhydramnios
  - Urinary tract abnormalities

### CT Scan

- Show dilated stomach and first part of the duodenum
- Show normal caliber colon
- In case of complete obstruction, small and large bowel is collapsed

### Upper Gastrointestinal Contrast Study

It is indicated in patients who have partial obstruction to proximal duodenum and is only modestly dilated.

### Fiberoptic Endoscopy

It is indicated in older children and adults may show the presence or absence of duodenal stenosis or wet.

Echo, radiograph of chest and spine is done to evaluate the associated defects.

#### GENERAL FEATURES

- Bilious vomiting
- Icterus

### TREATMENT

The initial treatment of infants with duodenal atresia includes nasogastric or orogastric decompression and intravenous fluid replacement. Echocardiography, renal ultrasound, and radiology of the chest and spine should be performed to evaluate for associated anomalies. Definitive correction of the atresia is usually postponed until life-threatening anomalies are evaluated and treated.

Treatment includes naso-oro-gastric decompression and intravenous fluid replacement. Definitive correction of atresia is usually postponed to evaluate and treat the life-threatening-associated anomalies.

The typical surgical repair for duodenal atresia is duodenoduodenostomy. This is done to bypass the obstruction. A distal proximal bowel is tapered in an attempt to improve peristalsis. A gastrostomy tube may be placed to drain stomach and protect the airway. The prognosis is primarily dependent upon presence of associated anomalies. This procedure is also preferred in cases of concomitant or isolated annular pancreas. In these instances, the duodenoduodenostomy is performed without dividing the pancreas. The dilated proximal bowel might have to be tapered to improve peristalsis.

Operative treatment includes transverse right upper quadrant supraumbilical incision. Direct duodenostomy—standard side-to-side fusion, diamond-shaped duodenostomy. Simple duodenal web may also be excised through a longitudinal, taking care that not to damage ampulla. If the proximal duodenum is excessively floppy or distended, an antimesenteric tapering duodenoplasty is done using the autostapling device. Postoperatively, duodenal ileum may take as long as 5–12 days to settle down. Postoperatively, a gastrostomy tube can be placed to drain the stomach and protect the airway. Intravenous nutritional support or a transanastomotic jejunal tube is needed until an infant starts to feed orally.

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# Gastroesophageal Reflux

## PRESENTING COMPLAINTS

A 10-week-old baby was brought with the complaint of frequent vomiting since 15 days.

### History of Presenting Complaints

A 10-week-old baby was brought to the pediatric outpatient department (OPD) with history of frequent vomiting. Her mother noticed that her daughter used to vomit as soon as she was given feeds. Later doctor was explained the mother proper technique of feeding as well as burping. In spite of proper technique baby used to vomit regularly about 3–4 times a day. Vomitus used to contain curded milk. There was no mass or any peristaltic movements are seen over the abdomen after feeding.

### Past History of the Patient

The girl was first sibling of nonconsanguineous marriage. She was born at full term by normal delivery. She cried immediately after delivery. The birth weight of the child was 3 kg. There was no significant postnatal event. She was on breast milk on the 2nd day itself.

## EXAMINATION

The child was moderately built and nourished. Child was lying comfortably on examination table. Anthropometric measurements include the length was 58 cm (97th centile), the weight was 4.5 kg (70th centile), and head circumference was 40 cm.

She was afebrile. Anterior fontanelle was normal. Heart rate was 110 per minute, respiratory rate was 28 per minute, and blood pressure recorded was 60/46 mm Hg. There was no pallor, no edema and no lymphadenopathy. All the systemic and general examinations were normal.

## INVESTIGATION

Hemoglobin	: 10 g/dL
TLC	: 7,000 cells/cu mm
DLC	: P <sub>65</sub> L <sub>30</sub> M <sub>2</sub> E <sub>3</sub>
ESR	: 20 mm at the 1st hour
Barium swallow	: Showed the delayed emptying of the esophagus

## DISCUSSION

It is defined as an involuntary passage of gastric contents into the esophagus. The regurgitated gastric content may be saliva, ingested food and gastric secretion. It may contain pancreatic or biliary secretion that had earlier refluxed into the stomach. This is due to duodenogastric reflux.

Gastroesophageal reflux disease (GERD) is the most common esophageal disorder in children of all ages. Gastroesophageal reflux (GER) signifies the retrograde movement of gastric contents across the lower esophageal sphincter (LES) into the esophagus, which occurs physiologically every day in all infants, older children, and adults. Physiologic GER is exemplified by the effortless regurgitation of normal infants. The phenomenon becomes pathologic GERD in infants and children who manifest esophagitis-related symptoms, or extraesophageal presentations, such as respiratory symptoms or nutritional effects.

Gastroesophageal reflux is the spontaneous passage of gastric contents into the esophagus.

### CASE AT A GLANCE

#### Basic Findings

Length	: 58 cm (97th centile)
Weight	: 4.5 kg (70th centile)
Temperature	: 37°C
Pulse rate	: 110 per minute
Respiratory rate	: 28 per minute
Blood pressure	: 60/46 mm Hg

#### Positive Findings

##### History

- Vomiting

##### Examination

- Normal

##### Investigation

- Barium swallow: Shows delayed emptying of esophagus



When it reaches the mouth, it is also called regurgitation. GER is a normal physiologic process that occurs throughout the day in healthy infants, children, and adults. When GER causes bothersome symptoms, GER becomes GERD. The signs and symptoms that have been attributed to GERD range from chest pain and heartburn to cough and pneumonia.

The muscular layer distal to the mid-esophagus is composed of smooth muscle fibers. Hence, it is not under voluntary control. The esophagus is hollow muscular tube. The peristaltic wave involving the external circular muscle layer is the force that propels the ingested food through the esophagus into the stomach.

The LES at the distal end of the esophageal peristalsis will transport food into the stomach. The LES is suspected to be abnormal in people who have GER. The more recent concept suggests that, LES may have episodes of transient relaxation, unassociated with esophageal peristalsis. Hence, it allows gastric contents to reflux into the esophagus.

Basal tone of LES at rest is independent of neurotransmitters. Relaxation of LES is mediated by inhibitory neurotransmitter. These are released from enteric neurons. Vasoactive intestinal peptide is one of the mediators. LES is tonically contracted at rest. This is abnormal in this disease. The basal tone is low. There will be episodes of transient relaxation unassociated with esophageal peristalsis, thus allowing gastric contents to reflux into the esophagus.

## **PATHOPHYSIOLOGY**

Gastroesophageal reflux occurs when the lower esophageal sphincter relaxes and allows the gastric contents to enter the esophagus.

The LES, defined as a high-pressure zone by manometry, is supported by the crura of the diaphragm at the gastroesophageal junction, together with valve-like functions of the esophagogastric junction anatomy, form the antireflux barrier. In the context of even the normal intra-abdominal pressure augmentations that occur during daily life, the frequency of reflux episodes is increased by insufficient LES tone, by abnormal frequency of LES relaxations, and by hiatal herniation that prevents the LES pressure from being proportionately augmented by the crura during abdominal straining.

There are three main types of reflux (acidic with a pH of <4, weakly acidic with a pH of 4–7, and nonacid reflux with a pH of >7). In pediatrics, the convention is to designate all reflux with a pH greater than 4 as nonacid because it cannot be detected by pH sensors in the esophagus.

The type of esophageal reflux varies depending on the timing of the reflux episode relative to a meal; reflux episodes in the 1–2 hours after a meal are typically weakly or nonacidic and those occurring 3–4 hours or more after a meal are predominately acidic. Infants, who only drink formula or breast milk every 2–3 hours, are almost always refluxing nonacidic formula/breast milk, which may explain the lack of efficacy of acid suppression to improve crying and fussiness. Understanding the type of reflux present in patients is critical in order to tailor therapies appropriately.

While acidic reflux has been associated with symptoms as well as signs such as dental erosions, esophagitis, and strictures, nonacid reflux, to date, has been associated only with symptoms including extraesophageal symptoms such as cough, wheezing, and pneumonia.

Half of all infants between 0 and 3 months of age and two-thirds of 4–6-month-old infants regurgitate at least once per day. The prevalence of regurgitation decreases dramatically after 8 months of age, which coincides with the introduction of solid food and the increase in time in the upright position. After 12 months of age less than 10% of children continue to have daily regurgitation, and new onset reflux beyond this age group requires careful consideration for other diagnoses, because the prevalence is low. While regurgitation in infants is common and not typically pathologic in otherwise thriving, happy infants, the more complex problem that the clinician faces is the infant who regurgitates and has symptoms of fussiness crying, and arching.

Infant reflux becomes evident in the 1st few months of life, peaks at 4 months, and resolves in up to 88% by 12 months and in nearly all by 24 months. Symptoms in older children tend to be chronic, waxing and waning, but completely resolving in no more than half, which resembles adult patterns. Genetic linkage is indicated by the strong evidence of GERD in studies with monozygotic twins. A pediatric autosomal dominant form with otolaryngologic and respiratory manifestations has been located to chromosome 13q14, and the locus is termed GERD1.

Reflux may occur with increased abdominal pressure. Chronically lax sphincter is the most important mechanism. The factors contributing to the competence of LES include abdominal position of sphincter, angle of insertion of esophagus into the stomach and sphincter pressure. Refluxed material is returned to the stomach by the secondary peristaltic wave in the esophagus. Swallowed saliva neutralizes and washes away the last traces of acid with primary peristaltic wave.



## CLINICAL FEATURES (FIG. 1)

Beyond infancy, more typical symptoms of heartburn, chest pain, and epigastric pain begin to predominate. In children between 3 and 9 years of age, typical symptoms are reported in 2–7% of patients with the most common symptom being epigastric pain. In adolescents, 5% of teens report symptoms of heartburn, epigastric pain, or regurgitation.

Clinical features are directly related to the exposure of esophageal epithelium to refluxed gastric content. Most of the infants (85%) will have vomiting during the 1st week of life. Some may have symptoms by 6 weeks. Patients with cerebral palsy, Down syndrome will have an increased incidence of reflux. In 60%, symptoms disappear by 2 years. But the remainder will have symptoms tilt the age of 4 years.

Infantile reflux manifests more often with regurgitation (especially postprandially), signs of esophagitis (irritability, arching, choking, gagging, feeding aversion), and resulting failure to thrive; symptoms resolve spontaneously in the majority of infants by 12–24 months. Older children can have regurgitation during the preschool years; this complaint diminishes somewhat as children age, and complaints of abdominal and chest pain supervene in later childhood and adolescence.

*The respiratory presentations are also age dependent:* GERD in infants can manifest as obstructive apnea or as stridor or lower airway disease in which reflux complicates primary airway disease such as laryngomalacia or bronchopulmonary dysplasia. Otitis media, sinusitis, lymphoid hyperplasia, hoarseness, vocal cord nodules, and laryngeal edema have all been associated with GERD.

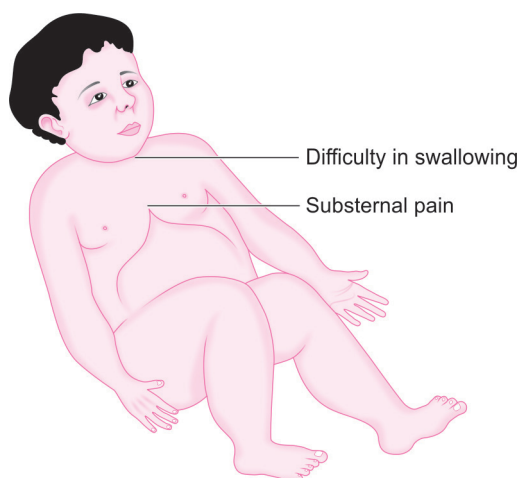


Fig. 1: Clinical features.

Airway manifestations in older children are more commonly related to asthma or to otolaryngologic disease such as laryngitis or sinusitis.

In young infants, many episodic events like apneic spells, “colic” crying, and sleep disturbances have been attributed to GER disease with or without esophagitis. Abnormal posturing with tilting of the head to one side and bizarre contortions of the trunk has been seen in some children with reflux. This symptom complex is referred as “Sandifer’s syndrome”.

Children with pathological GER present with failure to thrive. This is because from the loss of calories, symptoms attributable to esophagitis or with the episode event like apnea in young infant. The hallmark of the severe disease is failure to thrive. This occurs as a consequence of calorie loss due to the vomited volume.

It is good to differentiate between vomiting and regurgitation. Vomiting is the forceful expulsion of the gastric contents through the mouth. It has three distinct phases, i.e., nausea, retching and emesis. The emesis involves intense muscular activity of the respiratory and abdominal muscles. Regurgitation is an effortless passive bringing up of gastric contents involves no muscular activity.

The aspiration of gastric content leads to the inflammation and edema of the larynx and trachea. GER should be considered as a possible cause of recurrent respiratory symptoms. Recurrent bronchopulmonary infection and chronic asthma has been associated with GER.

### ESSENTIAL DIAGNOSTIC POINTS

- Involuntary passage of gastric contents into the esophagus
- The lower esophageal sphincter is abnormal
- Failure to thrive
- Recurrent respiratory symptoms
- Recurrent bronchopulmonary infection and chronic asthma
- Aspiration pneumonia

### SYMPTOMS POSSIBLY RELATED TO REFLUX ESOPHAGITIS

- Epigastric or retrosternal pain (heartburn)
- General irritability in infants (“colic”)
- Weight loss and/or failure to thrive
- Hematemesis and melena
- “Noncardiac angina-like” chest pain
- Symptoms related to iron-deficiency anemia
- Dysphagia (due to esophagitis and/or structure formation)
- Belching and postprandial fullness

Aspiration pneumonia occurs in about 30% of patients. In childhood, chronic cough, wheezing and recurrent pneumonia are common. Growth and weight gain are affected in about 60% of patients.

Iron deficiency anemia is noted among 25% of the patients. About two-thirds of the patients have delayed gastric emptying and vomiting because of the pylorospasm.

The major manifestation of esophagitis is hemorrhage. Hematemesis occurs in some children. Substernal pain is less common. Dysphagia may cause irritability and anorexia in advanced cases. Reflux may rarely cause laryngospasm apnea and bradycardia.

#### GENERAL FEATURES

- Regurgitation of food
- Cough
- Failure to gain weight
- Esophagitis

### DIFFERENTIAL DIAGNOSIS

- Hiatus hernia
- Tracheoesophageal fistula
- Esophagitis

### DIAGNOSIS

#### Upper Gastrointestinal Radiography

Barium imaging should only be used to diagnose anatomic abnormalities predisposing to reflux (e.g., hiatal hernia), to diagnose complications of reflux such as stricturing, or to look for GERD masqueraders (e.g., achalasia, pyloric stenosis, malrotation).

#### Barium Swallow

Contrast (usually barium) radiographic studies of the esophagus and stomach using barium has been used to study GER. While a barium study is not specific enough in evaluating the severity of GER, it would rule out such other structural abnormalities like a large hiatus hernia, esophageal stricture, duodenal web or an atypical pyloric stenosis and gastric outlet or intestinal obstruction.

#### pH Probe Study

pH probes were considered by many to be the gold standard test to confirm a diagnosis of GERD. These pH probes are inserted through the nose into the esophagus where the catheter remains with the pH sensor tip in the distal esophagus for approximately 24 hours. The catheter measures the number and duration of acid reflux episodes that have a pH of less than 4. Patients record symptoms during the test, and the time of these symptoms is correlated with esophageal reflux events present either before or after the symptom.

Currently, the role for pH probes are (1) to measure the total amount of acid reflux in a 24-hour

period to clarify the role of acid in esophagitis, dental erosions, and other acid-related complications; (2) to determine how much acid reflux is still present in patients taking acid suppression medications at the time when the pH probe is performed; or (3) to correlate symptoms with acid reflux events. Because the ambient pH of the esophagus is 5 or greater, it is not possible for pH sensors to reliably discriminate reflux with a pH greater than 4 from ambient esophageal pH.

#### Multichannel Intraluminal Impedance with pH

As with pH probes, multichannel intraluminal impedance with pH (pH-MII) catheters are also inserted through the nose into the esophagus. Unlike pH probes, there are seven impedance sensors distributed along the catheter, so bolus flow can be assessed at six different heights (between paired sensors). There is also an additional distal pH sensor on the catheter so that the pH of the refluxate can be determined.

The pH-MII test offers significant advantages over a pH probe alone, in that the catheters can (1) measure the directionality of flow, which allows for the differentiation of swallowed versus refluxed contents; (2) measure both acidic and nonacidic gastric contents; and (3) measure both distal and proximal reflux using sensors located throughout the esophagus.

The role of pH-MII in the evaluation of GERD is (1) to determine the temporal relationship between acid and nonacid reflux events and typical and atypical symptoms; (2) to determine the relationship between full column reflux and extraesophageal symptoms; (3) to determine the efficacy of acid suppression medications when pH-MII is performed while taking medications; and (4) to diagnose the relationship between symptoms and reflux events in patients with a greater nonacidic reflux burden.

#### Manometry

Esophageal manometry to assess pressure profile and their dynamic changes has not been proven helpful in practical management of GER and remains primarily a research tool today.

#### Scintigraphy

The goal of nuclear scintigraphy (also known as a milk scan or gastric emptying scan) is to determine the rapidity with which food or liquid empties from the stomach to determine, it delays in gastric emptying may contribute to worsening of GERD. Although the test is looking for triggers of reflux

(e.g., delayed emptying), it is not used to diagnose reflux itself. This test evaluates the degree to which isotope-labeled formula or food empty from the stomach following a 10-minute meal. Whenever possible, solid food is given during the test because delays in emptying are more often seen with solid food compared to liquid meals. Results are reported as either the percentage of meal remaining in the stomach after a fixed amount of time (usually 1 hour or hours).

Radionucleotides like  $^{99m}\text{Tc}$  added to the infant's feed can be monitored with a gamma counter and the time and amount of radionucleotide refluxed into the esophagus or lungs as well as the gastric emptying time can be studied. It has the advantage of being noninvasive and low in radiation.

## Endoscopy and Biopsy

### *Upper Endoscopy with Biopsy of the Esophagus*

The main role of endoscopy in the evaluation of patients with possible GERD is to assess for complications of GERD (e.g., erosions, Barrett esophagus, strictures), to treat strictures with balloon dilation, and to differentiate reflux esophagitis from eosinophilic esophagitis (EoE), the latter of which can present with symptoms identical to reflux, but the therapies differ greatly, so making the correct diagnosis is critical.

Currently, the indication for endoscopy in patients with suspected GERD is (1) to evaluate for masqueraders of reflux (e.g., infectious esophagitis, EoE) in patients not responsive to acid suppression therapy; (2) to evaluate and treat complications of GERD, such as Barrett esophagus or stricturing, and (3) to assess for anatomic abnormalities (e.g., hiatal hernia, slippage of Nissen fundoplication). Definitive diagnosis of GERD by endoscopy requires the presence of erosive esophagitis with endoscopically visible breaks in the esophageal mucosa.

The flexible fiberoptic and video endoscope enables direct visualization of the esophageal mucosa as well as study the dynamics of the LES. Although macroscopic evidence of esophageal ulceration strongly suggests reflux esophagitis, a mucosal biopsy is required to diagnose the less severe lesions.

Endoscopy allows diagnosis of erosive esophagitis and complications such as strictures or Barrett esophagus; esophageal biopsies can diagnose histologic reflux esophagitis in the absence of erosions while simultaneously eliminating allergic

and infectious causes. Endoscopy is also used therapeutically to dilate reflux-induced strictures.

Laryngotracheobronchoscopy evaluates for visible airway signs that are associated with extra-esophageal GERD, such as posterior laryngeal inflammation and vocal cord nodules.

Strictures are usually demonstrated with barium esophagography. Severe esophagitis may be suspected when ragged mucosal outline is seen on roentgenogram. But esophagography with biopsy is the superior technique. The severity and frequency of reflux can be documented for monitoring esophageal pH with probe in distal esophagus.

Esophageal mucosa for microscopic study can be obtained either by endoscopic pinch biopsy or suction biopsy. Since esophagitis tends to occur in a patchy distribution, visual inspection is important before taking a biopsy even though suction biopsy is more widely used. Increased number of biopsies from different areas will significantly improve the yield for microscopic diagnosis.

Histological criteria for the diagnosis of esophagitis on endoscopic biopsies have been graded. Basal cell zone hyperplasia of the esophageal squamous epithelium and increased stromal papillary length (Reflux-associated squamous hyperplasia—RASH) are the most commonly used criteria.

### LABORATORY SALIENT FINDINGS

- Barium swallow
- pH probe study
- Esophageal manometry
- Scintigraphy
- Flexible fiberoptic and video endoscope enables direct visualization of the esophageal mucosa as well as study the dynamics of the LES
- Suction biopsy
- *Histological criteria:* Basal cell zone hyperplasia of the esophageal squamous epithelium and increased stromal papillary length (Reflux-associated squamous hyperplasia—RASH)

## TREATMENT

There are two main goals of treatment: (1) to alleviate the symptoms of GERD and/or (2) to prevent complications of GERD. The choice of therapy depends on which goal is being addressed. In the patient with esophageal atresia, the goal may be to prevent reflux esophagitis and Barrett esophagus in adulthood. In contrast, the goal of treatment in an infant with spitting up and poor weight gain may be to reduce the regurgitation in the short term to prevent loss of calories from the regurgitation.

The main nonpharmacologic therapies in infants and children include positioning and dietary interventions. In infants, several well designed

studies have consistently shown that while right-side-down positioning may speed gastric emptying. Therefore, for infants monitored in hospital settings, left-side-down positioning is superior for reflux control. However, because of the concern that patients will roll into the prone positioning, side positioning is not recommended for infants unmonitored at home. Similarly, while prone positioning does seem to have the lowest rates of reflux of all of the positioning options, because of the risk of sudden infant death syndrome (SIDS), prone positioning cannot be recommended.

Another nonpharmacologic therapy frequently used is thickening agents added to formula or included in formula in the form of rice starch. While formulas with added rice starch require gastric acid to trigger the thickening in the stomach, the addition of cereal directly to the bottle thickens the formula instantly; adding thickening in this manner treats both GERD and oropharyngeal dysphagia. Typical thickening from a reflux perspective includes the addition of one teaspoon of rice cereal per ounce of formula, but the nipple should not be cut to accommodate the thickened formula, as this increases the risk of aspiration during swallowing.

Another common cause for reflux symptoms is infant overfeeding, where patients are fed too much volume or too frequently because the symptoms of fussiness, restlessness, and discomfort are misinterpreted as hunger.

Finally, the method of administering feeds may help with reflux control. In neurologically compromised patients or in patients with significant pulmonary symptoms, transpyloric feeding has been proposed as a means to control GERD. Pediatric studies support that transpyloric feeding reduces reflux episodes to the same degree as fundoplication, and outcome studies suggest that, at least with respect to extraesophageal symptoms, transpyloric feeding has equivalent outcomes to fundoplication as well. Therefore, in patients at high risk for surgery, for patients in whom it is not clear if symptoms are reflux related, in patients with gastric dysmotility, or as a parental preference, transpyloric feeding may serve as either a diagnostic or therapeutic intervention for GERD.

Gastroesophageal reflux is the involuntary passage of gastric contents into the esophagus. It produces esophagitis or respiratory complications. Factors such as thoracic stomach hiatal hernia, lack of intra-abdominal esophagus and loss of cardioesophageal angle results in incompetence of gastroesophageal sphincter mechanism. Endoscopy with flexible fiberoptic instrument

will detect esophagitis and potential stricture formation as well excludes the other causes such as enteropathy.

Medical therapy is better in infants than in older children. In uncomplicated cases, keeping the child prone, thickening the feeding with cereal, and careful attention at the time of burping are enough.

Conservative therapy and lifestyle modifications that form the foundation of GERD therapy can be effectively implemented through education and reassurance for parents. Dietary measures for infants include normalization of any abnormal feeding techniques, volumes; and frequencies. Thickening of feeds increases the percentage of infants with no regurgitation, decreases the frequency of daily regurgitation and emesis, and increases the infant's weight gain. However, caution should be exercised when managing preterm infants because of the possible association between xanthan gum-based thickened feeds and necrotizing enterocolitis.

A combination of modified feeding volumes, hydrolyzed infant formulas, proper positioning, and avoidance of smoke exposure satisfactorily improve GERD symptoms in infants with GERD. Older children should be counseled to avoid acidic or reflux-inducing foods. Weight reduction for obese patients and elimination of smoke exposure are other crucial measures at all ages.

Some evidence suggests a benefit to left side position and head elevation during sleep. The head should be elevated by elevating the head of the bed, rather than using excess pillows, to avoid abdominal flexion and compression that might worsen reflux.

Regurgitation being common during infancy, only those with GER. Disease should be selected for therapy. Treatment should be in a phase schematic manner. Small frequent feeds are useful, since they reduce the volume available in the stomach for reflux. Continuous nasogastric drip feeding is an effective means of ensuring catchup growth in severe cases. However, if weight gain does not occur after a week of nasogastric feeding, there is little benefit in continuing it.

The mainstays of therapy for GERD are acid suppression medications, either histamine receptor antagonists or proton pump inhibitors (PPIs).

Pharmacotherapy is directed at ameliorating the acidity of the gastric contents or at promoting their abnormal movement, and should be considered for those symptomatic infants and children who are either highly suspected or proven to have GERD. Antacids are the most commonly used antireflux therapy.

Histamine-2 receptor antagonists ( $H_2$ RAs: cimetidine, famotidine, nizatidine, and ranitidine) are widely used antisecretory agents that act by selective inhibition of histamine receptors on gastric parietal cells. There is a definite benefit of  $H_2$ RAs in treatment of mild-to-moderate reflux esophagitis.  $H_2$ RAs have been recommended as first-line therapy because of their excellent overall safety profile, but they are superseded by PPIs in this role.

Ranitidine (5–10 mg/kg/day in 2–3 divided doses) and cimetidine have been used extensively, with the former being better tolerated and having less adverse effects. Sucralfate is comparable to  $H_2$ RAs in efficacy in adults, but its safety and usefulness in children is unproven. Omeprazole, a gastric PPI has recently been reported effective in children with severe esophagitis refractory to  $H_2$  blockers. It may be given a trial before surgical treatment is decided.

Antireflux effect by blocking the hydrogen-potassium adenosine triphosphatase channels of the final common pathway in gastric acid secretion. PPIs are superior to  $H_2$ RAs in the treatment of severe and erosive esophagitis. The use of PPIs to treat infants and children deemed to have GERD on the basis of symptoms is now the standard of care. Omeprazole (0.7–3.3 mg/kg/day, max 80 mg), lansoprazole (1–3 mg/kg/day max 60 mg) and esomeprazole (<20 kg: 5–10 mg. >20 kg: 10–20 mg OD).

Prokinetic agents have some role in treatment. Domperidone, a dopamine receptor blocker is marginally beneficial, and is not widely used to treat reflux during infancy. Cisapride a 5-HT<sub>4</sub> antagonist is effective without many side effects and is thought to work by enhancing neurotransmitter release that stimulates smooth muscle contraction throughout the intestinal tract.  $H_2$  blockers do not decrease the frequency and duration of the reflux, but act by reducing the acidity of the gastric contents. Prokinetic agents available metoclopramide (dopamine-2 and 5-HT<sub>4</sub> antagonist), bethanechol (cholinergic agonist), and erythromycin (motilin receptor agonist). Most of these increase LES pressure; some improve gastric emptying or esophageal clearance.

## **SURGERY**

If the symptoms do not respond to a 6-week trial of intensive medical therapy, then surgical treatment is indicated.

The surgery done is Nissen fundoplication, is effective therapy for intractable GERD in children, particularly those with refractory esophagitis or strictures and those at risk for significant

morbidity from chronic pulmonary disease. It may be combined with a gastrostomy for feeding or venting. Preoperative accuracy of diagnosis of GERD and the skill of the surgeon are two of the most important predictors of successful outcome.

Surgical procedures aim to tighten the LES and thus prevent reflux of gastric contents into the esophagus. Nissen fundoplication which involves a 360° wrap of the fundus around the distal 3.5 cm of the esophagus in a common procedure. It is more commonly done for neurologically impaired children with severe GERD, and the results are comparable to that in normal children.

Recent reports suggest that an anterior gastric fundoplication may be equally effective. However, postoperative adhesions leading to small intestinal obstruction occur in 5–10% of cases after fundoplication.

Fundoplication procedures may be performed as open operations, by laparoscopy, or by endoluminal (gastroplication) techniques. Pediatric experience is limited with endoscopic application of radiofrequency therapy (Stretta procedure) to a 2–3 cm area of the LES and cardia to create a high-pressure zone to reduce reflux.

## **Follow-up Management**

The first follow-up endoscopy in those with esophagitis should be performed 4–12 weeks after instituting medical treatment. If the esophagus is normal,  $H_2$  blockers may be discontinued. Prokinetics, can be continued for longer periods depending on the symptomatic improvement.

Persisting esophagitis is an indication for contemplating surgery. However, since surgery is not free of complications, and GER in infants improves with age, the surgical option should be exercised only after all medical therapies has been exhausted.

Small frequent feeds are useful since they reduce the volume available in the stomach for reflux.

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## PRESENTING COMPLAINTS

A 5-year-old boy was brought with the complaints of:

- Fever since 1 week
- Vomiting since 3 days
- Abdominal pain since 3 days
- High-colored urine since 2 days

## History of Presenting Complaints

A 5-year-old boy presented with the history of fever, vomiting and abdominal pain. The boy was apparently normal till a week ago. To start with he developed the fever. Fever was moderate to high degree, intermittent more in the evening. There was associated history of vomiting. Vomiting was associated with nausea and was insidious. Boy was not tolerating any food and even water. Along with this, boy developed pain in abdomen. The pain

was present in right upper abdomen. He was not allowing anybody to touch the abdomen. There was history of passing of high colored urine.

## Past History of the Patient

He was the only child of the nonconsanguineous marriage. He was born at full term with normal delivery. He cried immediately after delivery. His birth weight was 3 kg. He was breastfed exclusively for 3 months. Weaning started later with cereals and completed by 1 year. His developmental milestones were normal. His performance at school was good.

## EXAMINATION

The boy was moderately built and moderately nourished. Signs of mild dehydration were present. This child was looking sick. His anthropometric measurements included the height 108 cm (75th centile), the weight was 14 kg (50th centile).

The child was febrile, i.e., 38°C. The heart rate was 110 per minute. Respiratory rate was 20 per minute. Blood pressure recorded was 80/60 mm Hg. The child was pale and icterus was present. There was no lymphadenopathy and no edema.

Per abdomen examination revealed presence of tender hepatomegaly. Liver was palpable about 3 cm below the costal margin, soft and tender. Tenderness was present at the right upper quadrant. Cardiovascular and respiratory system was normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 7,600 cells/cu mm
DLC	: $P_{78} L_{22} E_0 M_0$
ESR	: 22 mm at 1st hour
AEC	: 436 cells/cu mm
Serum bilirubin	: 7 mg/dL
Alkaline phosphatase	: 150 U/L
SGOT	: 60 U/L
SGPT	: 150 U/L
X-ray chest	: Normal

### CASE AT A GLANCE

#### Basic Findings

Height	: 108 cm (75th centile)
Weight	: 14 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 110 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 80/60 mm Hg

#### Positive Findings

##### History

- Fever
- Abdominal pain
- Vomiting
- High-colored urine

##### Examination

- Febrile
- Jaundice
- Sign of dehydration
- Tender hepatomegaly

##### Investigation

- Pallor
- Abdominal LFT
- Alkaline phosphatase: Increased
- SGOT: Increased
- SGPT: Increased



## DISCUSSION

Viral hepatitis (VH) is an important health problem in developing and developed countries of the world. Despite the availability of vaccines and prophylactic measures and improved sanitation, its incidence is almost constant. This can be explained with better understanding about epidemiological findings with changes in human ecology and behavior.

Hepatitis A virus (HAV) infection occurs throughout the world, but is most prevalent in developing countries. About 30–40% of the adult population have evidence of previous HAV infection. Hepatitis A is thought to account for approximately 50% of all clinically apparent acute viral hepatitis.

Hepatitis A virus infection is the most prevalent hepatotropic virus. This virus is also responsible for most forms of acute and benign hepatitis; although fulminant hepatic failure can occur.

Six major viruses are the etiologic agents responsible for most clinical cases of VH: HAV, hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (delta agent, HDV), hepatitis E virus (HEV), and hepatitis G virus (HGV). Recently hepatitis F virus (HFV) has been reported as a double-stranded deoxyribonucleic acid (DNA) virus. Various other causes of hepatitis are other viruses, drugs, toxins, bacteria, parasite and other noninfectious disorders.

## ETIOLOGY

Hepatitis A virus is a single-stranded ribonucleic acid (RNA) virus that is classified as a picornavirus. HAV causes acute hepatitis and asymptomatic infection, but never chronic infection.

Infection occurs primarily via the fecal-oral route because the virus is relatively resistant to gastric acidity, making it an extremely efficient gastrointestinal pathogen. Travel to countries where HAV is endemic is also a frequent cause of sporadic infection. In countries where it is endemic, infection is usually acquired in childhood and is most of the time asymptomatic.

These are more common in developing countries, where the prevalence rate approaches 100% in children by the age of 5 years. HAV causes only acute hepatitis and there is no complication once the acute attack subsides.

## PATHOPHYSIOLOGY

Hepatitis A virus spreads by person-to-person contact and by fecal oral route. Rarely parenteral transmission during viremia has been reported

in the prodromal period. Fecal excretion of virus occurs till late in the incubation period, while, at peak just before the onset of symptoms, and at minimum a week after the onset of jaundice. HAV is highly contagious. Transmission is almost always by person-to-person contact through the fecal-oral route. Perinatal transmission occurs rarely. No other form of transmission is recognized.

The mean incubation period for HAV is approximately 15–50 days. Fecal excretion of the virus starts late in the incubation period, reaches its peak just before the onset of symptoms, and resolves by 2 weeks after the onset of jaundice in older subjects. The duration of viral excretion is prolonged in infants. Incubation period ranges from 15 to 50 days while mean period being about 4 weeks. Food borne and waterborne outbreaks are common in crowded or unsanitary area.

Faeces is infectious from 2 weeks before and 1 week after the onset of jaundice. Viremia is evident from the 2nd to 6th week after the exposure. A patient is infectious in the prodromal stage, 1–2 weeks prior to illness. The risk of transmitting HAV is greatest from 2 weeks before to 1 week after the onset of jaundice. Infectivity falls rapidly with the onset of jaundice. Infective material is mainly feces, blood and sweat.

A period of viremia precedes the presence of virus in stool and continues through the period of elevated liver enzymes. Clinical disease occurs after shedding in stool has begun. The period of peak infectivity is during 2 weeks prior to jaundice or elevated alanine aminotransferase (ALT) and alkaline phosphatase, when the viral titer in the stool can be as high as, 10 infectious particles per milliliter. Shedding of virus can persist for several months in young children, presumably due to physiologic immunodeficiency.

Increased risk of infection is found in contacts with infected persons, childcare centers, and household contacts. Infection is also associated with contact with contaminated food or water and after travel to endemic areas. Common source foodborne and waterborne outbreaks have occurred, including several caused by contaminated food.

The human cases are the only reservoir of the infection. The cases range from asymptomatic infection to severe form. The asymptomatic, i.e., an icterus are especially common in children. There is no evidence of chronic carrier state.

## PATHOLOGY

Damage to liver is by way of hepatocyte damage, cholestasis and metabolic dysfunction. Hepatocyte damage is evidenced by release of aminotransferases

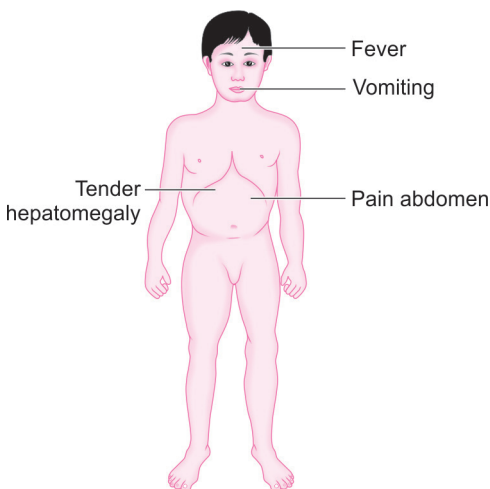
into the blood stream. Cholestasis is evident by elevation of serum alkaline phosphatase, serum nucleotidase and urinary urobilinogen. Metabolic dysfunction results in changes in ammonia, carbohydrate and drug metabolism.

The acute response of the liver to HAV is similar in all (A through E) hepatitis viruses. The entire liver is involved with necrosis and increased cellularity. Lobular architecture remains intact although balloon degeneration and necrosis of parenchymal cells occur initially. Diffuse Kupffer cell hyperplasia is also present along with infiltration of polymorphonuclear leukocytes and eosinophils. In neonates giant cell are seen. During complication of fulminant hepatic failure, there is total destruction of hepatic parenchyma.

Liver cell damage is most marked in the centrilobular region. Damage to hepatocytes is mediated by cell-mediated immune response. Some individual lobules are variably affected. Hepatocytes have a swollen granular appearance. Dead one become shrunken and deeply stained. They form eosinophilic bodies by losing their nuclei. These are called councilman bodies. These are strong indications of viral hepatitis. The portal tracts are enlarged and contain mononuclear cell infiltrate. Severe damage is accompanied by collapse of the reticulin framework especially between central vein and portal tract. Spleen and lymph nodes may also be enlarged. During viremia myocarditis, pancreatitis and intestinal ulceration may occur.

## CLINICAL FEATURES (FIG. 1)

The incubation period is 15–50 days with an average of 25–30 days. The onset is generally acute.



**Fig. 1:** Clinical features.

During the prodromal phase, the patient has moderate fever, loss of appetite, malaise, nausea, and upper abdominal pain. After the prodromal phase patient passes dark-colored urine.

Hepatitis A virus is responsible for acute hepatitis only. Often, this is an anicteric illness, with clinical symptoms indistinguishable from other forms of viral gastroenteritis, particularly in young children.

The illness is much more likely to be symptomatic in older adolescents or adults, in patients with underlying liver disorders, and in those are immunocompromised. It is characteristically an acute febrile illness with an abrupt onset of anorexia, nausea, malaise, vomiting, and jaundice. The typical duration of illness is 7–14 days.

Other organ systems can be affected during acute HAV infection regional lymph nodes and the spleen may be enlarged. The bone marrow may be moderately hypoplastic, and aplastic anemia has been reported. Tissue in the small intestine might show changes in villous structure, ulceration of the gastrointestinal tract can occur, especially in fatal cases. Acute pancreatitis and myocarditis have been reported, though rarely, and nephritis, arthritis, vasculitis, and cryoglobulinemia can result from circulating immune complexes.

Jaundice is not visible or is so mild that it can hardly be appreciated on clinical examination and can be detected by laboratory test only. Dark-colored urine may also be noticed after the systemic symptoms. Icterus is seen in sclera and skin will remain for 1–4 weeks. Liver is enlarged and tender. Splenomegaly is present in some cases. Recovery is usual. The mortality is less than 1%.

### ESSENTIAL DIAGNOSTIC POINTS

- Fever, chills, headache
- Fatigue, generalized weakness followed by anorexia, nausea, vomiting
- Dark-colored urine and jaundice
- Spreads by person-to-person contact and by fecal-oral route
- Infective material is mainly feces, blood and sweat
- Spleen and lymph nodes are enlarged

This disease is heralded by nonspecific symptoms such as fever, chills, headache, fatigue, generalized weakness followed by anorexia, nausea, vomiting, dark-colored urine, and jaundice. The disease is benign with complete recovery in several weeks. The case fatality rate is less than 0.1% usually from acute liver failure.

Sometimes atypical course includes cholestatic hepatitis characterized by jaundice and

severe pruritus. In most of them, symptoms resolve in 2–3 weeks after the onset and almost all patients recover completely. No chronic infection and carrier state will occur. In patients with acute hepatitis certain features may suggest fever, coryza, headache, photophobia, and cough.

Single exposure to the virus produces a humoral response and provides lifelong immunity. HAV has a single serotype.

#### GENERAL FEATURES

- Jaundice
- Anorexia
- Loss of weight

### DIAGNOSIS

Hepatitis A virus should be suspected when there is a history of infective hepatitis in family members, school friends or other close contacts or child has traveled to hepatitis endemic areas. Diagnosis is made by liver function tests, serologic criteria and virus isolation.

Basic investigations, such as urine for bile salts, bile pigments are done. Liver function tests reveal elevated ALT, AST, bilirubin, alkaline phosphatase, 5-nucleotidase and  $\gamma$ -glutamyl transpeptidase. Prothrombin time may also be elevated. These tests do not help to differentiate the type of hepatitis. Serum glutamic pyruvic transaminase (SGPT) levels are very high in the 1st week of illness. Serum glutamic oxaloacetic transaminase (SGOT) is moderately elevated. Prothrombin time is a useful test for assessing prognosis, Complete blood counts, blood glucose, urea, creatinine, total protein and albumin are checked when the child is hospitalized. Hepatitis is diagnosed only if the transaminases are more than twice the upper limit of normal. In viral hepatitis, ALT is markedly increased more than 20 times the upper limit of normal and is higher than AST indicating cytoplasmic rather than mitochondria injury.

The transaminase level remains elevated for 1–3 weeks. Serological tests for the diagnosis of hepatitis A are available. Anti-HAV is detected from onset of symptoms and persists throughout life. For initial 3–12 months anti-HAV (IgM) is detected and later on anti-HAV (IgG) is present.

Investigations for etiology are not necessary unless there are atypical manifestations or the child is hospitalized. All children should be screened for HBsAg. The presence of anti-HAV IgM or anti-HEV IgM confirms the diagnosis of acute HAV and HEV hepatitis respectively, HBsAg positivity along with anti-HBc IgM indicates acute

HBV hepatitis; whereas anti-HCV IgM positivity indicates acute HCV hepatitis.

Infection due to nonhepatotropic viruses, such as measles, parvovirus B<sub>19</sub>, herpes simplex 1 and 2, dengue virus, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV) may present with jaundice and moderate elevation of transaminases. The associated clinical features of the underlying illness and specific serologic tests will help in diagnosis. Other causes of hepatitis such as leptospirosis, typhoid fever, Wilson disease (WD) and autoimmune hepatitis should be excluded if there are atypical manifestations or features suggestive of nonviral hepatitis.

Ultrasound examination is done to exclude liver abscess or gallstones. Liver biopsy is not recommended in children with but is essential in those with suspected acute or chronic liver disease or chronic hepatitis.

Acute HAV infection is diagnosed by detecting antibodies to HAV, specifically, anti-HAV (immunoglobulin [Ig] M) by radioimmunoassay or, rarely, by identifying viral particles in stool. A viral polymerase chain reaction (PCR) assay is available for research use.

- Demonstration of HAV particles or specific viral antigens in the faeces.
- Demonstration of rise in anti-HAV titer.
- Detection of IgM antibody to HAV in patients' serum. This antibody appears early in illness persists for limited time usually for 3–4 months of life after the onset. IgG antibody indicates past infection and immunity.

Laboratory evaluation of liver function includes estimation of total and direct bilirubin, transaminases, alkaline phosphatase, prothrombin time, total protein and albumin.

### COMPLICATIONS

The complications include fulminant hepatic failure, relapse, cholestatic hepatitis, hyperbilirubinemia, aplastic anemia, renal failure, chronic hepatitis, and cirrhosis.

#### LABORATORY SALIENT FINDINGS

- Demonstration of HAV particles or specific viral antigens in the faeces.
- Demonstration of rise in anti-HAV titer.
- Detection of IgM antibody to HAV in patients serum.
- Serum glutamic pyruvic transaminase (SGPT) levels are very high in the 1st week of illness.
- Serum glutamic oxaloacetic transaminase (SGOT) is moderately elevated.

## TREATMENT

Hepatitis A virus infection is benign in children and all recover completely. Rarely fulminant hepatic failure can occur.

There is no specific treatment for acute hepatitis. Bed rest is recommended. Good nutrition rich in carbohydrate and supplied with adequate protein should be given. There is no role of corticosteroids as it may interfere with immunologic defenses. This leads to prolongation of convalescent phase and to chronic active hepatitis.

## PREVENTION

Patients infected with HAV are contagious for 2 weeks before and approximately 7 days after the onset of jaundice and should be excluded from school, childcare, or work during this period. Careful hand-washing is necessary, particularly after changing diapers and before preparing for serving food. In hospital settings, contact and standard precautions are recommended for 1 week after onset of symptoms.

Infection in children confers lifelong immunity. It is almost always asymptomatic or with mild symptoms and rarely culminating into fulminant hepatitis.

Indications for HAV vaccine are travelers going to areas of high prevalence, high risk population living in crowded areas, drug users, etc., residents of communities of HAV epidemics.

## Passive Immunization

Passive immunization is by immunoglobulin-serum (IgG). It is effective in prevention of HAV infection preferably early in incubation period in the dose of 0.02 mL/kg intramuscularly. It provides protection for 3 months.

Development of an inactivated HAV vaccine which is highly immunogenic and safe is a major breakthrough in prevention of hepatitis A.

In addition to active immunization hepatitis A infection can be prevented by passive immunization by the administration of IgG intramuscularly, but for short period only and by enteric precautions to check the further spread of HAV.

## Active Immunization

### *HAV Vaccine*

Recently, HAV vaccine is available for human use. This inactivated vaccine is prepared in cell culture and treated with formalin. Though hepatitis A infection in children confers lifelong immunity and is almost always asymptomatic or with mild

symptoms and rarely culminating into fulminant hepatitis in contrast to adults in whom disease occurs in severe form, vaccination of children is useful because these children can become carriers of the disease and could infect older siblings and adults.

Vaccination of young children in endemic areas is presently not recommended and universal childhood HAV immunization is under consideration. The dose of HAV vaccine for children aged 2–18 years is 360U (enzyme-linked immunosorbent assay units) intramuscular for each of the two initial injections, 1 month apart, followed by a booster 6–12 months after the first injection.

## Immunoglobulin

Indications for intramuscular administration of immunoglobulin (0.02 mL/kg) include preexposure and postexposure prophylaxis.

Immunoglobulin is recommended for pre-exposure prophylaxis for susceptible travelers to countries where HAV is endemic, and it provides effective protection for up to 3 months. HAV vaccine given any time before travel preferred for preexposure prophylaxis in healthy persons, but Ig ensures an appropriate prophylaxis in children younger than 12-month-old, patients allergic to a vaccine component. If travel is planned in <2 weeks, older patients, immunocompromised hosts, and those with chronic liver disease or other medical conditions should receive both Ig and the HAV vaccine.

Immunoglobulin prophylaxis in postexposure situations should be used as soon as possible (not effective more than 2 weeks after exposure). It is exclusively used for children younger than 12-month-old, immunocompromised hosts, those with chronic liver disease or in whom vaccine is contraindicated.

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# Hirschsprung's Disease

## PRESENTING COMPLAINTS

An 8-year-old boy was brought with the complaints of:

- Persistent soiling since 5 years
- Constipation since 5 years

## History of Presenting Complaints

An 8-year-old boy came with history of persistent soiling. But on no occasion, he had smeared or passed the feces. He had bowel disorder of constipation. He was responding to simple laxatives. Boy was on laxatives many a time. Bowel training later proved very difficult and approximately every 3 months, he was receiving rectal wash-out. This was temporarily improving his incontinence. He never responded to medical management.

## Past History of the Patient

He was the first child of consanguineous union. He was delivered at term by normal pregnancy.

Baby cried immediately after delivery. There was no significant postnatal event. From the beginning, he had problem with bowel habits. He was having alternate loose motion and constipation. He was discharged on the 5th day. Child did not pass motion for 5 days and infant was readmitted at 10 days. No abnormalities were found. Constipation was relieved by laxatives. Other developmental milestones were normal. His school performance was good. He was not popular in school and had few friends.

## EXAMINATION

Child was moderately built and moderately nourished. Anthropometric measurements included the height was 120 cm (50th centile) and weight was 20 kg (50 centile). He was afebrile, pulse rate was 96 per minute. The respiratory rate was 20 per minute. The blood pressure recorded was 90/70 mm Hg. There was no pallor, no lymphadenopathy, no icterus and no clubbing.

Per abdomen examination revealed presence of distension. No organomegaly, bowel sounds were sluggish. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 7,600 cells/cu mm
DLC	: P <sub>68</sub> L <sub>24</sub> E <sub>4</sub> M <sub>2</sub> B <sub>2</sub>
Platelet count	: 3,00,000 cells/cu mm
X-ray abdomen	: Narrow segment with dilated colon above
Barium enema	: Showed the evidence of a change in the caliber between rectum and sigmoid colon
Rectal manometry	: Absence of normal relaxation
Rectal biopsy	: Absence of ganglion cells in submucosa

### CASE AT A GLANCE

#### Basic Findings

Height	: 120 cm (50th centile)
Weight	: 20 kg (50th centile)
Temperature	: 36.8°C
Pulse rate	: 96 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 90/70 mm Hg

#### Positive Findings

##### History

- Persistent soiling
- Constipation
- Used laxatives

##### Examination

- Distension of abdomen

##### Investigation

- *X-ray abdomen*: Narrow segment with dilated colon above
- *Barium enema*: Change with caliber between the rectum and sigmoid colon
- *Rectal biopsy*: Absence of ganglion cells in submucosa



## DISCUSSION

Child had experienced the problem since the 1st week of life for passing the stools. He required laxative at that time. This suggests organic pathology. In case of long duration of soiling, the child should have either functional constipation or ultrashort segment, i.e., Hirschsprung's disease. A full thickness biopsy of anal sphincter was performed. This confirmed the presence of aganglionic ultrashort segment leading to diagnosis of Hirschsprung's disease. Patient became continent within 3 months and remained so.

It is the most common cause of lower intestinal obstruction in neonates, with an overall incidence of 1 in 5,000 live births. The male-female ratio for Hirschsprung's disease is 4:1 for short segment disease.

It is the most important cause of neonatal obstruction. It results absence of ganglion cells in the bowel wall or failure of migration of embryonic neural crest cells into the bowel wall or failure of cranio-caudal extension of mesenteric and submucous plexus within the wall. In the affected segment, sympathetic overactivity results in hypertension and absence of appropriate relaxation in response absence of ganglion cells in the bowel wall or failure of migration of embryonic neural crest cells into the bowel wall or failure of cranio-caudal extension of mesenteric and submucous plexus within the wall to proximal distension.

Hirschsprung disease, or congenital aganglionic megacolon, is a developmental disorder (neurocristopathy) of the enteric nervous system, characterized by the absence of ganglion cells in the submucosal and myenteric plexus. It is caused by sphincture abnormal innervation of the bowel, beginning in the internal anal and extending proximally to involve variable length of the gut.

Migration of the neuroenteric cells occur cranio-caudally. Migration of cells from Auerbach's to other plexus take place. Role of neural glycoproteins includes that of—fibronectin and laminar proteins. Vagal neural crest cells—the only source of ganglion cells. There is abnormally large amount of laminin in extracellular spaces, and hence there is decreased ability of ganglion cells to adhere to smooth muscle cells. There is lack of cell-to-cell adherence.

There is an increased familial incidence in long-segment disease. Hirschsprung's disease may be associated with other congenital defects, including trisomy 21, Goldberg-Shprintzen syndrome, Smith-Lemli-Opitz syndrome, cartilage-hair hyperplasia, multiple endocrine neoplasm 2

syndrome, neurofibromatosis, neuroblastoma, and urogenital or cardiovascular abnormalities.

## PATHOLOGY

Hirschsprung's disease is the result of an absence of ganglion cells in the bowel wall, extending proximally and continuously from the anus for variable distance. The absence of neural innervation is a consequence of arrest of neuroblast migration from the proximal to distal bowel. Without the myenteric and submucosal plexus, there is inadequate relaxation of the bowel wall and bowel wall hypertonicity, which can lead to intestinal obstruction.

Aganglionic segment is limited to rectosigmoid in 80% of patients. In 15% colon is aganglionic from anus to hepatic flexure. Incomplete parasympathetic innervation in aganglionic segment results in abnormal peristalsis, constipation and functional intestinal obstruction. Proximal to transverse bowel, muscular hypertrophy thickens the intestinal wall. The intestine may become enormously dilated with retained feces and gas.

Histologically, there is an absence of Meissner's and Auerbach's plexuses and hypertrophied nerve bundles with high concentrations of acetylcholinesterase between the muscular layers and in the submucosa.

## PATHOPHYSIOLOGY

There is increase in adrenergic and cholinergic innervation. Adrenergic excitatory activity predominates. There is increased smooth muscle tone. There is loss of nitric oxide synthetase from mesenteric plexus. There is imbalance of smooth muscle contractility.

Aganglion produces colonic stasis leading to the bacterial overgrowth enteroadherent bacteria attach to unprotected intestinal epithelium. This leads to invasion of bacteria into the epithelium. Inflammatory process leads to clinical enterocolitis, systemic sepsis and coagulopathy set in.

## CLINICAL FEATURES (FIG. 1)

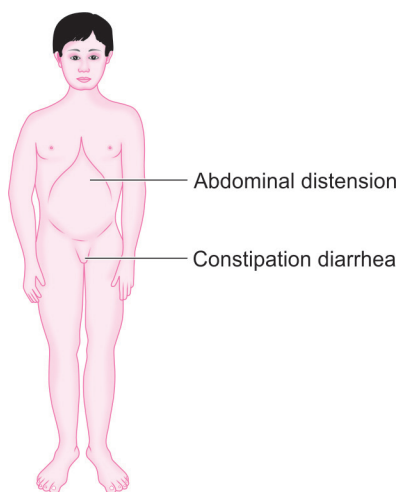
About 99% of full-term infants pass meconium within 48 hours of birth. This disease is suspected in any full-term infant with delayed passage of stool.

Hirschsprung's disease is usually diagnosed in the neonatal period secondary to a distended abdomen, failure to pass meconium, and/or bilious emesis or aspirates with feeding intolerance. In 99% of healthy full-term infants,



meconium is passed within 48 hours of birth, Hirschsprung's disease should be suspected in any full-term infant (the disease is unusual in preterm infants) with delayed passage of stool. Some neonates pass meconium normally but subsequently present with a history of chronic constipation. It may manifest in 1st week of life as partial or complete obstruction with vomiting and abdominal distension (**Fig. 2**). This is associated with poor feeding and bilious vomiting. Temporary relief may be seen after rectal examination. Diarrhea may be prominent in neonatal period and may be associated with symptoms of intestinal obstruction. Hypoproteinemia and edema may result.

Failure to pass stool leads to dilatation of the proximal bowel and abdominal distension. Intraluminal pressure increases as bowel dilates. This leads to the decreased blood flow and deterioration of mucosal barrier. Stasis allows proliferation of bacteria, which can lead to enterocolitis (*Clostridium difficile*, *Staphylococcus aureus*,



**Fig. 1:** Clinical features.



**Fig. 2:** Abdominal distension.

anerobes, coliforms) with associated diarrhea, abdominal tenderness, sepsis and signs of bowel obstruction. Early recognition of Hirschsprung's disease before the onset of enterocolitis is essential in reducing morbidity and mortality. This may be associated with septicemia and bowel obstruction.

In neonates, Hirschsprung's disease must be differentiated from meconium plug syndrome, meconium ileus, and intestinal atresia.

Episodes of constipation or diarrhea may alternate with periods of apparent normality. In older children, it may cause chronic constipation and abdominal distension. A large fecal mass is palpable in left lower abdomen. But on rectal examination, rectum is usually empty.

Hirschsprung's disease in older patients must be distinguished from other causes of abdominal distention and chronic constipation. In older patients, the Currarino triad must be considered, which includes anorectal malformations (ectopic anus, anal stenosis, imperforate anus), sacral bone anomalies (hypoplasia, poor segmentation), and presacral anomaly (anterior meningoceles, teratoma, cyst).

The history often reveals constipation starting in infancy that has responded poorly to medical management. The abdomen is tympanic and distended, with a large fecal mass palpable in the left lower abdomen. Rectal examination demonstrates a normally placed anus that easily allows entry of the finger but feels snug. The rectum is usually empty of feces, and when the finger is removed, there may be an explosive discharge of foul-smelling feces and gas. The stools, when passed, can consist of small pellets, be ribbon-like, or have a fluid consistency, unlike the large stools seen in patients with functional constipation. Intermittent attacks of intestinal obstruction from retained feces may be associated with pain and fever.

#### ESSENTIAL DIAGNOSTIC POINTS

- Abnormal innervation of the bowel, beginning in the internal sphincter.
- There is decreased ability of ganglion cells to adhere to smooth muscle cells.
- Absence of ganglion cells in the bowel wall.
- Clinical enterocolitis, systemic sepsis and coagulopathy set in.
- Failure to pass stool leads to dilatation of the proximal bowel and abdominal distension.
- Associated with septicemia and bowel obstruction.
- On rectal examination, rectum is usually empty.

Diarrhea may fulminate into enterocolitis producing profound dehydration and shock with

fluid and electrolyte loss into the lumen of the obstructed bowel. *Clostridium difficile* has been implicated in etiology.

Features which raise the suspicion include poor growth and prominent abdominal distension with both gas and fecal retention. The abnormally increased anal tone may or may not be clinically detectable, and relatively empty rectum may also be an inconsistent feature.

#### GENERAL FEATURES

- Dilatation of the proximal gut
- Failure to thrive
- Dilated colon in radiography

### INVESTIGATION

Full blood count may detect iron deficiency anemia. Serum protein levels reveal hypoproteinemia. Anteroposterior and lateral plain abdominal radiographs confirm stool and gas retention. The absence of gas in rectal ampulla favors Hirschsprung's disease.

### Radiographic Studies

- *Plain X-ray abdomen:* Severely distended loops of intestine. Relative paucity of air levels in the location of rectum force air under diaphragm (perforation of proximal intestine). Air-fluid level suggestive of obstruction.
- *Barium enema:*
  - Spastic distal segment with a dilated proximal intestine
  - Zone transition
  - Incomplete evaluation of barium—24 hours postevacuation of radiograph
  - In enterocolitis, evidence of edema, spasm and ulceration of intestinal wall.

Barium enema on unprepared colon may define the transition area between the normally innervated, dilated colon, and aganglionic narrow segment. Other diagnostic findings are:

- An abrupt change in caliber between ganglionic and aganglionic sections of the bowel.
- Irregular saw-tooth contraction of aganglionic segment.
- Parallel transverse folds in dilated proximal colon.
- A thickened nodular edematous proximal colon associated with protein-losing enteropathy.
- Failure to evacuate barium.

Rectal examination demonstrates normal anal tone and is usually followed by explosive discharge of foul-smelling feces and gas.

Rectal suction biopsy is the gold standard for diagnosing Hirschsprung's disease. The biopsy material should contain an adequate amount of submucosa to evaluate for the presence of ganglion cells. To avoid obtaining biopsies in the normal area of hypoganglionosis, which ranges from 3 to 17 mm in length, the suction rectal biopsy should be obtained no closer than 2 cm above the dentate line. The biopsy specimen should be stained for acetylcholinesterase to facilitate interpretation. Patients with aganglionosis demonstrate a large number of hypertrophied nerve bundles that stain positively for acetylcholinesterase with an absence of ganglion cells between muscular layer and submucosa. Calretinin staining may provide a diagnosis of Hirschsprung's disease when acetylcholinesterase staining may not be sufficient.

Anorectal manometry evaluates the internal anal sphincter while a balloon is distended in the rectum. In healthy individuals, rectal distention initiates relaxation of the internal anal sphincter in response to rectal distention. In patients with Hirschsprung disease, the internal anal sphincter fails to relax in response to rectal distention. Although the sensitivity and specificity can vary widely; in experienced hands, the test can be quite sensitive.

#### LABORATORY SALIENT FINDINGS

- Rectal examination
- Rectal suction and biopsy
- Anorectal manometry
- Barium enema
- Plain X-ray abdomen
- Iron deficiency anemia
- Hypoproteinemia

It is measured by distension of balloon placed within rectal ampulla. It shows fall of pressure in the internal anal sphincter in normal individual. But there is striking rise in pressure in patients with megacolon.

### DIFFERENTIAL DIAGNOSIS

Differential diagnoses in newborn include meconium plug syndrome, hypothyroidism, septicemia and cystic fibrosis. Other diagnoses include aerophagia, subacute intestinal obstruction acquired megacolon, paralytic ileus and anal fissure.

### TREATMENT

Once the diagnosis is established, it is preferable to do limited laparotomy with multiple biopsies. Colostomy is done in the most distal portion of

normally ganglionated colon. Attempts to postpone surgery by repeated colonic irrigation until infant reaches satisfactory size are not justified of risk of enterocolitis.

Once the diagnosis is established, the definitive treatment is operative intervention.

There are three basic surgical options.

### Summary of Surgical Procedures

*Swenson's pull-through:* A two-layered circumferential colorectal anastomoses performed as low as possible to anocutaneous junction, thereby excising aganglionic segment nearly completely. The first successful surgical procedure, described by Swenson, was to excise the aganglionic segment and anastomose the normal proximal bowel to the rectum 1–2 cm above the dentate line. The operation is technically difficult and led to the development of two other procedures.

*Modified Duhamel's pull-through:* Disconnections of bowel at peritoneal reflection are involved. Pull through of the ganglionic colon through the incision made in posterior rectal wall about 1.5 cm from and margin orifice. Linear cutter stapler is used to cut and staple two opposing walls. Final outcome is creation of bowel, anterior wall made up of aganglionic rectum and posterior wall made up of pulled through ganglionic colon.

*Soave's endorectal pull-through:* The endorectal pull-through procedure described by Soave involves stripping the mucosa from the aganglionic rectum and bringing normally innervated colon through the residual muscular cuff, thus bypassing the abnormal bowel from within. Advances in techniques have led to successful laparoscopic

single-stage endorectal pull-through procedures which are the treatment of choice. Removal of mucus and submucosa of rectum and pulling ganglionic intestine through the aganglionic muscular cuff and an anastomoses at anus.

In ultrashort segmental disease, aganglionic segment is limited to internal sphincter. Excision of the strip of rectal muscle, including the internal and sphincter is diagnostic and therapeutic. When the entire colon is aganglionic ileal-anal anastomoses is the treatment of choice, preserving the part of aganglionic colon to facilitate water absorption. This helps stools to become firm.

Postoperative problems include recurrent enterocolitis, stricture, prolapse, perianal abscess and fecal soiling.

The prognosis of surgically treated Hirschsprung's disease is generally satisfactory; the great majority of patients achieve fecal continence. Long-term postoperative problems include constipation, recurrent enterocolitis, stricture, prolapse, perianal abscesses, and fecal soiling.

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# Intussusception

## PRESENTING COMPLAINTS

A 7-year-old boy was brought with the complaints of:

- Abdominal pain since 2 days
- Vomiting since 1 day
- Loose motion since 1 day

## History of Presenting Complaints

A 7-year-old boy was presented with the history of abdominal pain and profuse sweating. The abdominal pain was intermittent. It was diffuse and nonlocalized. Boy developed loose motions. After sometime loose motion was mainly mucus and blood stained. No fecal matter was present. Child became flushed with the pain in the abdomen and lower part of the chest. Simultaneously vomiting started. It was projectile in nature and vomitus was greenish and watery in nature.

### CASE AT A GLANCE

#### Basic Findings

Height	: 122 (75th centile)
Weight	: 21 kg (50th centile)
Temperature	: 37.2°C
Pulse rate	: 120 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 100/70 mm Hg

#### Positive Findings

##### History

- Abdominal pain, intermittent
- Vomiting
- Loose motion

##### Examination

- Flushed
- Sign of dehydration
- Mass felt in epigastrium
- Skin nodule
- Subcostal tenderness

##### Investigation

- Platelets: High
- ESR: High
- Barium enema: Filling defect in the midtransverse colon

## Past History of the Patient

He was the first sibling of the nonconsanguineous marriage. He was born at full-term with normal delivery. He cried immediately after delivery. There was no significant postnatal event. He was discharged on 3rd day. He was on breast milk exclusively for 4 months. Weaning started at 4 months and completed by 18 months. There was no delay in developmental milestone. There was no previous history of attack of loose motion and vomiting.

## EXAMINATION

The boy was moderately built and nourished. The boy looked flushed. There were signs of moderate dehydration. Anthropometric measurements included the height was 122 cm (75 centile), the weight was 21 kg (50th centile).

He was afebrile, the pulse rate was 120 per minute and respiratory rate was 20 per minute. The blood pressure recorded was 100/70 mm Hg. There was no pallor, no lymphadenopathy and no edema.

Per abdomen examination revealed presence of fullness in left upper quadrant and in left hypochondrium. There was no organomegaly. Bowel sounds were normal.

Other systemic examinations were normal. He had several birth marks including skin nodules. There was slight subcostal tenderness.

## INVESTIGATION

Hemoglobin	: 10 g/dL
TLC	: 15,000 cells/cu mm
DLC	: $P_{78} L_{20} E_2$
Platelet count	: 6,00,000 cells/cu mm
ESR	: 56 mm in the 1st hour
Blood urea	: 17 mg/dL
Total protein	: 4.2 g/dL
Total albumin	: 2.9 g/dL
Serum electrolytes	: Na—120 mEq/L K—4 mEq/L Cl—20 mEq/L
Barium enema	: Classical filling defect in the mid transverse colon

## DISCUSSION

Intermittent abdominal pain associated with fullness in the abdomen (**Fig. 1**) and is associated with blood-stained mucous stools. These symptoms suggest intussusception.

Intussusception occurs when one portion of proximal intestine telescopes into a more distal portion (intussusciens). Once this prolapse has occurred, lymphatic and venous congestion develops, resulting in edema, strangulation, ischemia, and ultimately necrosis. Additionally, the lumen of the intussuscepted portion of the bowel collapses, causing intestinal obstruction. Intussusception is fatal if spontaneous reduction does not occur and it is left untreated; therefore, prompt diagnosis and treatment are critical for successful management.

Intussusception occurs when a portion of the alimentary tract is telescoped into an adjacent segment. It is the most common cause of intestinal obstruction between 5 months and 3 years of age and the most common abdominal emergency in children younger than 2 years. Sixty percent of patients are younger than 1 year of age, and 80% of the cases occur before age 24 months; it is rare in neonates.

The incidence varies 1–4 per 1,000 live births. The male to female ratio is 4:1. If there is any underlying abnormality in GIT, this acts as a focus of the intussusception. The associated findings such as birth marks, skin nodules are seen in neurofibroma. These are known to be associated with increased risk of developing tumor. The boy developed non-Hodgkin lymphoma. Lymphomatous infiltration can result in thickening of intestinal lining. This may act as a basis for intussusception. The condition may complicate into otitis media, gastroenteritis and upper respiratory tract infection.



**Fig. 1:** Mass in upper abdomen—intussusception.

## PATHOGENESIS

Intussusception is the most common cause of intestinal obstruction in children under 2 years of age. While it may occur at any age, intussusception is uncommon prior to 3 months of age, and children ages 3 months to 3 years are most commonly affected. There is a peak in incidence between 5 and 7 months of age. Intussusception occurs twice as often in boys as in girls. Intussusception occurs twice as often in boys as in girls.

Pediatric intussusception is idiopathic (without an identifiable lead point) in 90% of cases. A majority of these cases are ileocolic. The mechanism is hypothesized to be an extra mucosal lead point such as Peyer's patch hypertrophy or mesenteric lymphadenitis. Viral gastroenteritis (most commonly adenovirus), Henoch-Schönlein purpura, intestinal lymphoid hyperplasia, and meconium ileus have all been associated with intussusceptions.

Only 10% of pediatric intussusception can be attributed to a pathologic lead point, which include Meckel diverticulum, intestinal polyps, intestinal duplication, hemangioma, suture line, appendix, tumors, and ectopic pancreas. Pathologic lead points should be suspected in children over 2 years of age with intussusception or in children with recurrent intussusceptions. In children with classic symptoms and normal contrast enema, small bowel to small bowel intussusceptions may be the culprit. Intussusception associated with a lead point is more likely to recur if the lead point is not excised.

Infection by concurrent respiratory adenovirus (type C) causes primary lymphoid hyperplasia or an enlarged hypertrophied ileal lymphoid patch. This then acts as leading point for intussusception.

Intussusception is noted in these conditions such as Henoch-Schönlein purpura, hemophilia, lymphoma, Peutz-Jeghar syndrome, leukemia and cystic fibrosis. Recurrent intussusception is seen among cystic fibrosis. Seasonal peak incidence when gastroenteritis and respiratory infection are common, i.e., rainy and cold season.

It is postulated that gastrointestinal infection or the introduction new food proteins results in swollen Peyer patches in the terminal ileum. Lymphoid nodular hyperplasia is another related risk factor. Prominent mounds of lymph tissue lead to mucosal prolapse of the ileum into the colon, thus causing an intussusception.

## PATHOLOGY

Intussusceptions are most often ileocolic, less commonly cecocolic, and occasionally ileal. The upper portion of bowel, the intussusceptum, invaginates into the lower, the intussusciens,



pulling its mesentery along with it into the enveloping loop.

Constriction of the mesentery obstructs venous return; engorgement of the intussusceptum follows, with edema, and bleeding from the mucosa leads to a bloody stool sometimes containing mucus. The apex of the intussusception can extend into the transverse, descending, or sigmoid colon, even to and through the anus in neglected cases. This presentation must be distinguished from rectal prolapse. Most intussusceptions do not strangulate the bowel within the first 24 hours but can eventuate in intestinal gangrene and shock.

It occurs when the portion of the alimentary tract is telescoped into the segment just caudal to it. The causes are unknown. The correlation with adenoviral infection is noted. Swollen Peyer's patches in the ileum stimulate intestinal peristalsis in an attempt to extrude the mass, thus causing intussusception.

There will be one leading point as the cause for the intussusception in 8–10% of cases. Recognizable lead points for the such as a Meckel diverticulum, intestinal polyp, neurofibroma, intestinal duplication cysts, inverted appendix stump, leiomyomas, hamartoma, ectopic pancreatic tissue, anastomotic suture line, enterostomy tube, post-transplant lymphoproliferative disease, hemangioma malignant conditions such as lymphoma, or Kaposi sarcoma. Lead points are more common in children older than 2 years of age, the child, the higher the risk of a lead point.

At ileum and ileocecal valve, there is greater disproportion in sizes. Hence, intussusception usually originates in the distal ileum and proceeds into the ascending colon. It can be either primary/secondary, simple/compound (intussusception of an intussusception).

## CLINICAL FEATURES (FIG. 2)

Intussusception should be included in the differential diagnosis of all children with intestinal obstruction. Infants may present with the classic triad of intermittent, crampy abdominal pain, palpable abdominal mass, and "currant jelly" stools, although the majority of children will not have all three of these symptoms at presentation. The early course is associated with sudden onset of severe paroxysms of abdominal pain.

Infant can present with diarrhea and colicky pain or restlessness alternating with listlessness without showing the pain. It may be possible to palpate typical sausage-shaped mass in the right upper abdomen. But this is often difficult in irritable child.

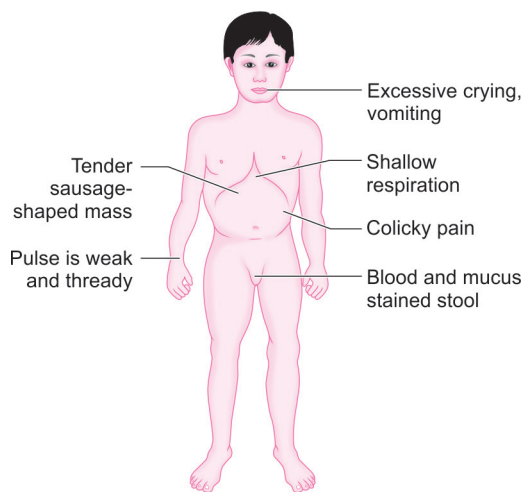


Fig. 2: Clinical features.

In typical cases, there is sudden onset, in a previously well child, of the severe paroxysmal colicky pain that recurs at frequent intervals and is accompanied by straining efforts with legs and knees flexed and loud cries. The infant may initially be comfortable and play normally between the paroxysms of pain; but if the intussusception is not reduced, the infant becomes progressively weaker and lethargic.

At times, the lethargy is disproportionate to the abdominal signs. Eventually shock like state may develop with the rise of body temperature, pulse becomes weak and thready, peritonitis, can develop. The respiration is shallow and grunting. The pain may be manifested only by moaning sounds.

Vomiting occurs in most cases and is usually more frequent in the early phase. In the later phase, the vomitus becomes bile stained.

Stools of normal appearance may be evacuated in the 1st few hours of symptoms. After this time, fecal excretions are small or more often do not occur, and little or no flatus is passed. Blood is generally passed in the first 12 hours, but at times not for 1–2 days, and infrequently not at all; 60% of infants pass a stool containing red blood and mucus, the currant jelly stool. The classic triad of pain, a palpable sausage-shaped abdominal mass, and bloody or currant jelly stool is seen in <30% of patients with intussusception.

Palpation of the abdomen usually reveals a slightly tender sausage shaped mass, sometimes ill defined, which might increase in size and firmness during a paroxysm of pain and is most often in the right upper abdomen, with its long axis cephalocaudal. If it is felt in the epigastrium, the long axis is transverse.



**ESSENTIAL DIAGNOSTIC POINTS**

- Intermittent abdominal pain with fullness in the abdomen
- Blood stained mucous stools
- Associated with Meckel's diverticulum, intestinal polyp, duplication and lymphosarcoma
- Mostly of ileocolic and ileoileocolic type
- Diarrhea and colicky pain or restlessness
- Typical sausage-shaped mass in the right upper abdomen

Chronic intussusception is more likely to occur with acute enteritis. It may occur in older children and as well as in infants.

Abdominal distension and tenderness develop as intestinal obstruction becomes more acute. Recurrent intussusception is more common after hydrostatic than surgical reduction.

**GENERAL FEATURES**

- Severe paroxysmal colicky pain
- Pain at frequent interval
- Shock

**DIAGNOSIS**

Plain abdominal radiograph reveals the density in the area of intussusception. A barium enema will show a filling defect or a cupping in the head of the barium. A thin rim of barium may be seen trapped around the invaginating intestine in the folds of mucosa within the intussusception. Reduction of intussusception is an emergency procedure.

In children with stable vital signs erect and supine plain abdominal radiograph shows characteristic signs of absence of gas in the cecum and ascending colon, a crescentic gas shadow at the apex of the intussusception and dilated loops of obstructed small intestine with fluid levels.

The central linear column of the barium may be visible in compressed lumen of the intussusception and a thin rim of barium may be seen trapped around the invaginating intestine in the folds of mucosa within the intussusception-coiled spring sign.

**LABORATORY SALIENT FINDINGS**

- Plain abdominal radiograph reveals the density in the area of intussusception.
- A barium enema will show a filling defect or a cupping in the head of the barium.
- A thin rim of barium may be seen trapped around the invaginating intestine in the folds of mucosa within the intussusception—coiled spring sign.
- Ultrasonography include a tubular mass in longitudinal view and doughnut or target appearance in transverse images.

Characteristic appearance of concentric rings or a large doughnut while scanning in right lower quadrant and moving clockwise around the abdomen. Concentric rim marks the mucosal or scroal interfaces in early intussusception. When the wall of the intussusception becomes edematous, its lumen is compressed and the intussusception becomes stretched around the mass. An axial cross-section of the bowel at this stage shows a round, thick walled doughnut. A longitudinal cross section shows an oval thick walled doughnut.

Abdominal ultrasound is the standard imaging modality for intussusception, with a diagnostic accuracy of approximately 85%. Cross-sectional ultrasonography of the intussusception reveals a target sign with concentric layers of serosa and mucosa, and on longitudinal views, the tip of the intussusceptum can be seen. A target sign may also be visible on abdominal computed tomography (CT) scan.

Saline enema under ultrasound guidance to monitor hydrostatic reduction is successful in nearly 95% cases acts as a part of treatment. Contraindication of nonoperative treatment includes signs of peritonitis, signs of gangrenous bowel, free gas under the diaphragm, multiple air fluids levels of X-ray.

*Maximum permissible height of barium:* It is 30 cm above the buttocks. Pressure should not exceed 120 cmH<sub>2</sub>O. Reduction must be done by surgeon along with radiologist.

*Signs of complete reduction:* These include barium entering the small bowel—terminal ileum, disappearance of mass which was initially palpable and passage of flatus and contrast through anus.

A negative filling defect and nonentrance of contrast in terminal ileum does not necessarily mean nonreduction. Edema at ileocecal valve junction leads to negative filling defect and prevents contrast of colon from entering small bowel. If the first attempt is unsuccessful, second attempt of hydrostatic reduction be done in 2–4 hours if the patient condition is stable.

The findings in ultrasonography include a tubular mass in longitudinal view and doughnut or target appearance in transverse images.

**DIFFERENTIAL DIAGNOSIS**

- Enterocolitis
- Meckel's diverticulum
- Anaphylactoid purpura

**COMPLICATIONS**

- Adhesions
- Internal herniation

- Septicemia
- Perforation
- Gangrene

## TREATMENT

The first-line treatment for ileocolic intussusception in a stable child is radiographic enema reduction.

Reduction of an acute intussusception is an emergency procedure and should be performed immediately after diagnosis in preparation for possible surgery. In 75% of cases where there is no prostration, shock or peritoneal irritation, it is possible to reduce by hydrostatic pressure with the fluoroscopic guidance. The success rate of radiologic hydrostatic reduction under fluoroscopic or ultrasonic guidance is approximately 80–95% in patients with ileocolic intussusception. Spontaneous reduction of intussusception occurs in approximately 4–10% of patients.

To confirm successful reduction of the intussusception, contrast must be observed to reflux-past the ileocecal valve into the distal ileum. Following successful reduction, about 8–15% of children will have recurrence of intussusception. Most recurrences are within 6 months with one-third occurring within the first 24 hours after reduction. A second attempt at nonoperative reduction is the preferred management of recurrent ileocolic intussusception and may be safely completed within a few hours.

If there is any evidence of obstruction with abdominal distension and in ileoileal type hydrostatic reduction should not be attempted, because of the risk of perforation of intussusception. In patients with prolonged intussusception and signs of shock, peritoneal irritation, intestinal perforation, or pneumatosis intestinalis, hydrostatic reduction should not be attempted.

Operative intervention is indicated if enema reduction has failed or contraindications to nonoperative reduction, such as perforation, peritonitis, or hemodynamic instability, are present. An operation is also necessary if a pathologic lead point is identified. The surgical management of intussusception begins with attempts at manual reduction. If reduction is successful and no pathologic lead points are identified, the operation is concluded. Bowel resection is required for bowel ischemic pathological lead point, or inability to manually reduce the prolapsed segment. Resection is followed by primary bowel anastomosis or

diversion, depending on the state of the child and the intestine. Traditionally, open reduction has been performed through a right lower quadrant abdominal incision, but the laparoscopic approach is becoming more popular.

Resection of intussusception with end to end anastomosis is done. Untreated intussusception in infants is almost always fatal. The chances of recovery are directly related to duration of intussusception before reduction.

Surgical treatment includes—Cope's maneuver, i.e., gentle passing of the finger on apex of intussuscepted intestine in the descending or transverse colon; breaking down the adhesion.

## PROGNOSIS

Untreated intussusception in infants is usually fatal; the chances of recovery are directly related to the duration of intussusception before reduction. Most infants recover if the intussusception is reduced in the 1st 24 hours, but the mortality rate rises rapidly after this time, especially after the 2nd day.

The recurrence rate after reduction of intussusceptions is approximately 10%, and after surgical reduction it is 2–5%; none has recurred after surgical resection. Most recurrences occur within 72 hours of reduction. Corticosteroids may reduce the frequency of recurrent intussusception. Repeated reducible episodes caused by lymphonodular hyperplasia may respond to treatment of identifiable food allergies, if present.

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## PRESENTING COMPLAINTS

A 10-year-old boy was brought with the complaints of:

- Fever since 7 days
- Loss of appetite since 5 days
- Abdominal pain since 3 days

## History of Presenting Complaints

A 10-year-old boy presented with a history of the severe abdominal pain. The pain was present in the right upper quadrant. The pain became worse during the last 24 hours. Pain was more in the night and there was disturbed sleep because of severe pain. Pain was not related to any food intake or to bowel habits. His mother noted that the appetite of the boy was reduced. There was no history of nausea and vomiting or diarrhea.

### CASE AT A GLANCE

#### Basic Findings

Height	: 135 cm (50th centile)
Weight	: 30 kg (50th centile)
Temperature	: 39.2°C
Pulse rate	: 126 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 80/60 mm Hg

#### Positive Findings

##### History

- Fever for 3 weeks
- Chills and rigors
- Pain in abdomen
- Decreased appetite

##### Examination

- Toxic
- Guarding
- Tenderness in right upper quadrant
- Tender hepatomegaly

##### Investigation

- *TLC*: Increased
- *ESR*: Increased
- *Alkaline phosphatase*: Increased
- *Ultrasound liver*: Large liver abscess
- Platelet count decreased

He was admitted to the hospital. On admission he was toxic and dehydrated. He was febrile, i.e., 39°C. There was moderate cervical lymphadenopathy. The hemoglobin was 12.3 g/dL. *TLC*: 11,700 cells/cu mm. Blood culture and sensitivity was sterile. He was observed in the hospital. Child became afebrile next day. Later he was discharged and advised bed rest. For about 15 days he was in bed rest. He had fever with night sweats but no rigors. The abdominal pain remained localized in the right upper quadrant. Pain started increasing in intensity and became almost continuous. This was producing disturbed sleep in night. There was no change in bowel and bladder habits.

## Past History of the Patient

The boy was the eldest sibling of the noncon-sanguineous marriage. He was born at full term by normal vaginal delivery. There was no significant postnatal event. Child had been on breast milk on the 2nd day. He was exclusively on breast milk for 6 months. Weaning started at 6 months and he was on family food by the age of 15 months. His developmental milestones were normal. He was immunized completely. His performance at school was good.

## EXAMINATION

He was moderately built and moderately nourished. He was looking toxic and dehydrated. Anthropometric measurements included his height was 135 cm (50th centile), weight was 30 kg. He was febrile. The pulse rate was 126 per minute. The respiratory rate was 26 per minute. The blood pressure recorded was 80/60 mm Hg.

There was no pallor, no lymphadenopathy and no cyanosis and clubbing. There was no icterus.

Per abdomen examination revealed enlarged liver. Liver was palpable about 3 cm below the costal margin. It was smooth and tender. There was tenderness and guarding in the right hypochondrium. Otherwise the abdomen was soft. Cardio-vascular and respiratory system examination were normal.

## INVESTIGATION

Hemoglobin	: 11.6 g/dL
TLC	: 11,700 cells/cu mm
DLC	: P <sub>72</sub> L <sub>18</sub> E <sub>6</sub> B <sub>2</sub> M <sub>2</sub>
Platelet count	: 6,00,000 cells/cu mm
Total protein	: 7.6 g/dL
Albumin	: 3.1 g/dL
Alkaline phosphatase	: 35.8 U/L
ESR	: 40 mm in the 1st hour
SGOT	: 50 U/L
SGPT	: 46 U/L
Ultrasound	: Shows the large liver abscess

## DISCUSSION

Acute illness of 3 weeks associated with the remittent onset of fever and enlarged tender hepatomegaly and associated with thrombocytopenia suggests liver disorder.

Liver abscesses are usually classified as pyogenic or amebic based on etiology. The distinction is important because treatment varies substantially. Important aspects of the patient's history that suggest amebic rather than pyogenic abscess include bloody diarrhea or travel to tropical areas preceding the illness.

Hepatic abscesses are caused by bacterial infections or amebiasis, *Echinococcus granulosus* and fungal infections are other rare causes of hepatic abscesses.

The major predisposing factors for the development of liver abscess are related to immunocompromised states. These include chronic granulomatous disease, acute leukemia, steroid therapy and recent attack of measles.

The factors associated with the development of pyogenic liver abscess (PLA) include peritoneal abscess, prematurity, supportive umbilical vessel thrombophlebitis, skin infection, bacteremia and surgical procedure for necrotizing enterocolitis.

Other factors which have been incriminated include malnutrition, bile duct ascariasis, trauma, aplastic anemia and sickle cell disease.

## PATHOGENESIS

Bacteria can reach the liver through various routes. These include contagious spread, portal vein routes, umbilical vessel and hematogenous spread. Hepatic abscess following pancreatitis, cholangitis, (subphrenic abscess) or penetrating trauma; and cryptogenic biliary tract infections are the examples of contagious spread.

Portal vein may carry the organism from the gastrointestinal tract to the liver. Hepatic abscess

that occur following pylephlebitis, intra-abdominal infection, or abscess secondary to appendicitis, inflammatory bowel disease, diverticulitis, enteritis, ulcerative colitis and omphalitis are the example for portal vein transmission.

Hematogenous spread is the common route by which hepatic abscess occur in children. Pyogenic hepatic abscess associated with bacteremia is an example. Umbilical vessel catheterization in the neonate can result in hepatic abscess.

Blunt trauma is known to result in liver abscess. Cryptogenic liver, where in no portal of entry can be delineated. They are thought to be caused by infection of infarcted portions of liver. The biliary tract disease or gastrointestinal infection usually brings the intestinal flora to the liver. Hence, abscess associated with these conditions are caused by gram negative enteric bacilli and anaerobic organism.

### ESSENTIAL DIAGNOSTIC POINTS

- Remittent onset of fever and enlarged tender hepatomegaly and associated with thrombocytopenia
- *Immunocompromised states*: Chronic granulomatous disease, acute leukemia, steroid therapy and measles
- Hematogenous spread is the common route
- In neonate, it is associated with fever, abdominal distension, abdominal tenderness, hepatomegaly, tachypnea and nuchal rigidity

## PATHOLOGY

The liver is enlarged. It shows solitary abscess or multiple abscesses. Solitary abscesses are more common than multiple abscesses. Right lobe of the liver is more commonly involved. Microscopically abscess shows disintegrating hepatocytes infiltrated by polymorphs. Areas remote from the abscess in the liver may reveal inflammation of portal tract.

Multiple abscesses are associated with ascending cholangitis give rise to spiking temperature. Prominent symptoms include fever, nausea, vomiting, anorexia, lassitude, weakness, diarrhea, weight loss, and abdominal pain.

Pyogenic hepatic abscess is polymicrobial. *Staphylococcus aureus* is the most common organism involved. It is especially found in the solitary abscess of children with chronic granulomatous disease. In contrast gram-negative enteric bacilli and anaerobic organism are frequently isolated when multiple hepatic abscess occur. *Klebsiella*, *Pseudomonas*, *E. coli*, *Enterobacter* and *Salmonella* have been isolated from these abscesses. Anaerobes such as *Streptococcus*, *Bacteroides fragilis*, *Fusobacterium* and *Brucella* have been identified.

## CLINICAL FEATURES (FIG. 1)

Patients with infections of the liver generally present with nonspecific symptoms such as fever, fatigue, abdominal pain, or weight loss. The abdominal pain may be diffuse, and confined to the right upper quadrant, or radiate to the shoulder or back. Other symptoms may include headache, arthralgias, and adenopathy.

A history of predisposing factors and tender hepatomegaly prompt for diagnosis. Signs and symptoms are nonspecific and can include fever, night sweats, malaise, fatigue, nausea, abdominal pain with right upper quadrant tenderness, and hepatomegaly; jaundice is uncommon. Fever and pain are present in the right upper quadrant. There is tender hepatomegaly. Rapidity of onset of the symptoms with the remittent fever points towards the bacterial sepsis followed by the collection of pus. Pus can be expected in the liver as there is hepatomegaly.

Forty percent of the cases are found in chronic granulomatous disease. Source of the infection may be from pyelephlebitis, generalized sepsis, cholangitis, and systemic spread from the cryptogenic biliary tract infection.

In neonate, it is associated with fever, abdominal distension, abdominal tenderness, hepatomegaly, tachypnea and nuchal rigidity.

## Amebic Liver Abscess

Amebic abscess presents similarly to PLA but is caused by *Entamoeba histolytica*. Jaundice is infrequently seen, and diarrhea may be seen in less than half of patients at the time of presentation;

however, a history of dysentery should raise suspicion for this disease.

As with PLA, the leukocyte count and erythrocyte sedimentation rate (ESR) are usually elevated, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase are normal to mildly elevated. Imaging studies should include ultrasound or CT of the abdomen.

Additional studies include evaluation of the stool for ova and parasites looking for trophozoites or cysts and testing the stool for *E. histolytica* antigen; note that stool tests may be negative in the case of extraintestinal amebiasis and that routine ova and parasite examination does not permit differentiation of *E. histolytica* from nonpathogenic *Entamoeba*.

Serologic testing of the blood is positive in >90% of patients. Many patients from endemic areas, however, will already have antibodies from previous exposure; the tests can also be falsely negative for the 1st day of infection. Aspiration of the abscess may also be used to distinguish between pyogenic and amebic liver abscess. In amebic liver abscess, the fluid is classically sterile and reddish-brown in color; amebic organisms will be seen in less than one-third of cases.

### GENERAL FEATURES

- Nonspecific symptoms
- Anorexia
- Jaundice
- Raised ESR

## DIAGNOSIS

Diagnosis can be challenging and is often delayed; a high index of suspicion is necessary in children with risk factors.

Routine laboratory studies may show abnormal results, but rarely are they diagnostic of PLA. Anemia and leukocytosis are common.

Liver function tests generally reflect underlying disease of the liver itself. Raised level of alkaline phosphates in serum could be indicative of underlying biliary tract obstruction or disease. Transaminase concentrations generally are normal to mildly elevated in majority of the cases. A rapidly enlarging, tender liver in a patient with normal transaminase concentrations should alert the clinician to the possibility of liver abscess. Serum aminotransferase and more often the alkaline phosphatase levels are elevated. The ESR is high, and leukocytosis is common. The results of blood cultures are positive in 50% of patients.

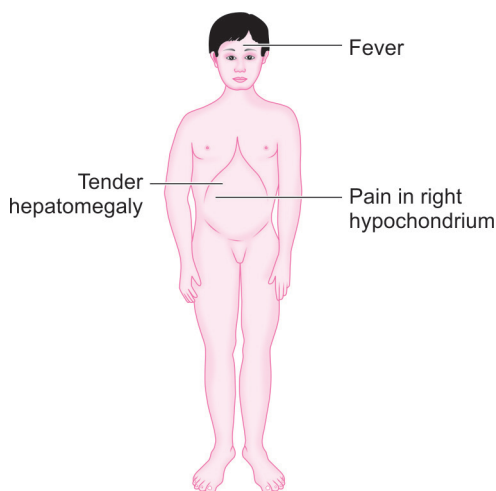


Fig.1: Clinical features.



Laboratory findings of liver infection often consist of leukocytosis, elevated ESR, and variable elevation of bilirubin, aminotransferases [(ALT), (AST)], alkaline phosphatase, and  $\gamma$ -glutamyl transferase (GGT). Liver ultrasound is useful in initial evaluation of suspected liver infection because it can screen for liver abscess or bile duct anomalies.

Chest X-rays might show elevation of the right hemidiaphragm with decreased mobility or a right pleural effusion.

Ultrasound and CT scan may be used to confirm the diagnosis of liver abscesses, to locate them for performing diagnostic or therapeutic drainage procedures under the guidance of images produced by them to study their evolution and response to therapy and also to document healing. However, they cannot be used with certainty for differentiating a PLA from an amebic liver abscess.

Radionuclide scans can be useful in the diagnosis of liver abscesses. Tc sulfur colloid liver scan is capable of detecting about 85% of lesions greater than 2 cm diameter. Anterior, posterior and lateral views reveal decreased isotope concentration in both pyogenic and amebic abscesses. Ga scans can reveal areas of increased isotope concentration of pyogenic abscess. Radionuclide scans, ultrasonography, CT scan and highly sensitive techniques for the detection of liver abscess.

If fluid is aspirated from the abscess cavity, it should be cultured aerobically and anaerobically. Blood culture may also show the causative organism in a great proportion of cases.

Solitary liver abscesses (70% of cases) in the right lobe of the liver (75% of cases) are more common than multiple abscesses or solitary left lobe abscesses. Enzyme-linked immunosorbent assay testing for *E. histolytica* Gal/GalNAc (galactose/N-acetyl-D-galactosamine) lectin in serum is usually positive with amebiasis.

#### LABORATORY SALIENT FINDINGS

- Anemia and leukocytosis are common
- Altered LFT
- Ultrasound and CT scan
- Radionuclide scans are aspirated fluid from the abscess cavity should be cultured aerobically and anaerobically
- Blood culture

#### COMPLICATIONS

Complications include pleuropulmonary involvement, peritonitis, subphrenic or subhepatic abscess, duodenal fistula and hemobilia.

#### DIFFERENTIAL DIAGNOSIS

- Subphrenic abscess
- Lung abscess
- Peritonitis
- Amebiasis

#### TREATMENT

The treatment modalities used in the management of PLA in children include antimicrobial therapy, needle aspiration, percutaneous catheter drainage and open surgical drainage. Antimicrobial therapy is the mainstay of management and is instituted alone or in combination with one or more surgical techniques.

##### Antimicrobial Therapy

In children, a combination of penicillinase-resistant penicillin, an aminoglycoside or a third generation cephalosporin seems suitable. The antimicrobial agents may have to be changed depending upon the clinical response and result of culture studies.

Antibiotic therapy should initially be broad spectrum but then narrowed, based on the culture results of the abscess fluid. Empirical initial antibiotic regimens include ampicillin/sulbactam, ticarcillin/clavulanic acid, or piperacillin/tazobactam. Others recommend combination of a third-generation cephalosporin plus metronidazole. Amebic abscesses are treated with metronidazole or tinidazole plus paromomycin (oral nonabsorbable to treat the associated intestinal amebic infection). Antibiotic therapy for pyogenic abscess is intravenous for 2–3 weeks followed by oral therapy to complete a 4–6 weeks course.

A combination of an aminoglycoside and a third-generation cephalosporin may have to be instituted on the basis of in vitro susceptibility testing of gram-negative enteric isolates. If an anaerobic organism is isolated, the clinician may have to select from penicillin, clindamycin, metronidazole, and chloramphenicol.

Penicillin is usually adequate for gram-positive anaerobic organisms or microaerophilic streptococci while the rest are effective against gram-negative anaerobes. The duration of therapy is undecided, but most accept that it should be prolonged over at least 4 weeks.

##### Percutaneous Aspiration

Percutaneous aspiration and drainage of an abscess is a simple procedure that can be used to confirm the diagnosis of PLA. Pus aspirated at the



procedure can be sent for microbiological testing. The results can be helpful in guiding antimicrobial therapy.

Percutaneous drainage under CT or USG guidance scores over surgical exploratory or open drainage as it decreases the morbidity associated with general anesthesia and surgical exploration. However, complications do occur. These include hemorrhage, falling off of drainage tube requiring reinsertion and migration of the tube into the pleura giving rise to sterile pleural effusion or empyema.

Abscess fluid should be obtained by either needle aspiration or placement of a drainage catheter. Specimens should be sent for Gram stain and culture. Gram-positive bacteria are most common in children, although gram-negative bacteria and anaerobes are frequently involved, and the specimen may grow more than one pathogen. Antibiotic therapy is aimed at covering the most likely pathogens and is then refined based on culture results and susceptibilities. Treatment parenterally for 4–6 weeks is generally recommended.

### Treatment of Amebic Liver Abscess

Treatment most often begins with metronidazole (50 mg/kg/day divided into three doses) for 10 days, with alternatives of tinidazole, ornidazole, and nitazoxanide, which can be given for shorter periods of time. This should then be followed by a luminal amebicide such as paromomycin or iodoquinol for 10 or 20 days, respectively. This combination is effective at eradication in >90% of patients. Surgery or invasive therapy usually is not needed. Aspiration may be indicated when

fever and abdominal pain persist after 4–5 days of treatment and in large abscesses with imminent risk of rupture. In these patients, repeated aspiration may be helpful in improving symptoms and speeding symptom resolution. Complications are generally related to delay in diagnosis or rupture of the abscess, which can cause peritonitis, as well as pulmonary or even cardiac involvement. Mortality is directly related to these findings.

### PROGNOSIS

The prognosis of the PLAs depends on the rapidity with which the diagnosis is made and treatment is started. Mortality has improved over the years to about 11–16% due to high index of suspicion that has resulted in early diagnosis and availability of better diagnostic (especially imaging) facilities.

Following treatment, abscesses usually resolve over 6 weeks. Recurrences, though infrequent, are known to occur. Polymicrobial bacteremia, hypoalbuminemia, multiple liver abscesses, presence of complications and an underlying immunodeficiency state are accompanied by an increased mortality in patients with PLA.

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# Necrotizing Enterocolitis

## PRESENTING COMPLAINTS

An 8-day-old boy was brought with the complaints of:

- Breathlessness since 5 days
- Distension of abdomen since 2 days
- Painful abdomen since 2 days

## History of Presenting Complaints

A male baby was born at preterm. It was delivered vaginally. The birth weight of the baby was 1.4 kg. Gestational age corresponds to 32 weeks. The Apgar score was 4 at one minute and 6 at five minutes. He developed respiratory distress and was shifted to neonatal intensive care unit (NICU). Child started improving without assisted ventilation. Standard low birth weight formula feed was given on 3rd day of life.

On the 8th day, distension of the abdomen was noted. Abdomen was painful on palpation. Feeding chart showed the presence of 5 mL of residual milk from the last feeding. Sister-in-charge

also noticed that higher incubator temperature was required to maintain body temperature.

## EXAMINATION

A low birth weight baby was lying sick in the incubator. Features of IUGR were present. There was distension of the abdomen. Anthropometric measurements included the length 45 cm (3rd centile), the weight 1.3 kg, and the head circumference was 32 cm.

Activity of the child was not satisfactory. Cry of the baby was not satisfactory. He was afebrile. The heart rate was 130 per minute. The respiratory rate was 40 per minute. The blood pressure recorded was 50/40 mm Hg.

Per abdomen examination revealed mild distension and was tender. Bowel sounds were sluggish. No organomegaly. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 14 g/dL
TLC	: 20,000 cells/cu mm
DLC	: $P_{88} L_{28} E_2 M_2 B_0$
Blood c/s	: Sterile
Urine c/s	: Sterile
Stool c/s	: Sterile
BT	: 6 minutes (1–6 minutes)
CT	: 5 minutes (4–8 minutes)
Platelet count	: 4,00,000 cell/cu mm
Peripheral blood smear	: Normal blood picture with leukocytosis
Serum electrolytes	: Na—120 mEq/L K—4 mEq/L Cl—98 mEq/L
Arterial blood gases	: pH—7.1 PaO <sub>2</sub> —65 mm Hg PaCO <sub>2</sub> —35 mm Hg HCO <sub>3</sub> —20 mEq/L
Erect abdomen X-ray	: Shows pneumatosis intestinalis

## CASE AT A GLANCE

### Basic Findings

Length	: 45 cm (3rd centile)
Weight	: 1.3 kg
Temperature	: 37°C
Pulse rate	: 130 per minute
Respiratory rate	: 40 per minute
Blood pressure	: 50/40 mm Hg

### Positive Findings

#### History

- Preterm baby
- Low birth weight
- Abdominal distension
- Residual milk

#### Examination

- Low birth weight
- Features of IUGR
- Abdominal distension sluggish, bowel sounds not active

#### Investigation

- Leukocytosis
- X-ray erect abdomen—pneumatosis intestinalis

## DISCUSSION

Necrotizing enterocolitis occurs among the premature infants who are undergoing stress in the 1st week of life. Clinically, it closely resembles that of septicemia. This is because of associations of abdominal distension, apnea, bradycardia, instability of temperature, cyanosis and lethargy.

Necrotizing enterocolitis (NEC) is a serious gastrointestinal disease that occurs primarily in preterm infants. The disease is characterized by the rapid onset of intestinal inflammation, various degrees of mucosal or transmural necrosis of the intestine and, in severe cases, can lead to intestinal necrosis and multiorgan dysfunctions that result in death. NEC has been reported as a complication of premature birth. It remains the most common gastrointestinal complication in preterm infants, and is a major cause of morbidity and mortality in neonates.

## PATHOLOGY AND PATHOGENESIS

Many factors may contribute to the development of the pathologic findings of NEC including necrotic segment of intestine, gas accumulation in the submucosa of the bowel wall (pneumatosis intestinalis), and progression of the necrosis to perforation, peritonitis, sepsis, and death. The distal part of the ileum and the proximal segment of colon are involved most frequently; in fatal cases, gangrene may extend from the stomach to the rectum.

Necrotizing enterocolitis in term infants is seen in infants with history of birth asphyxia, Down syndrome, congenital heart disease, rotavirus infections, and Hirschsprung's disease.

Necrotizing enterocolitis is a multifactorial disease primarily associated with intestinal immaturity. The triad of intestinal ischemia (injury), enteral nutrition (metabolic substrate), and bacterial translocation has classically been linked to NEC. The greatest risk factor for NEC is prematurity. The disorder probably results from an interaction between loss of mucosal integrity due to a variety of factors (ischemia, infection, inflammation) and the host's response to that injury (circulatory, immunologic, inflammatory), leading to necrosis of the affected area.

Clustering of cases suggests a primary role for an infectious agent. Various bacterial and viral agents, including *Escherichia coli*, *Klebsiella*, *Clostridium perfringens*, *Pseudomonas*, *Salmonella*, *Staphylococcus* astrovirus, norovirus, and rotavirus, have been recovered from cultures. Aggressive enteral feeding may predispose to the development

of NEC. Stasis of the intestinal contents favors the bacterial overgrowth.

It is characterized by partial or full thickness intestinal ischemia usually involving the terminal ileum. The risk factors include prematurity, neonatal stress, formula feedings, surgery in newborn, umbilical artery catheterization, septicemia and hypoalbuminemia.

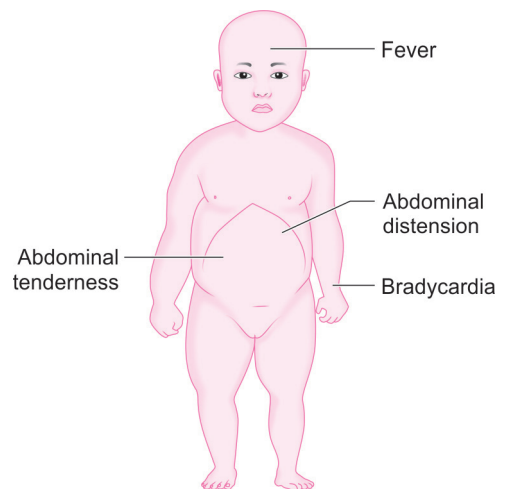
Several factors have been implicated. The two main factors are mucosal injury and formula feeding. Mucosal theory is attributed to ischemic damage to the intestinal mucosal barrier. This occurs as a result of fetal distress, perinatal asphyxia, respiratory distress syndrome, hypothermia, vascular spasm, or following exchange transfusions for hyperbilirubinemia. Mucosal injury is also attributed to diarrhea and infection. Infection produces injury to the gut.

Mucosal ischemia produces sloughing. Gas develops within the muscular layer. These may be seen as pneumocele in the X-ray. If full thickness necrosis occurs, perforation and peritonitis develops.

Almost all patients of necrotizing enterocolitis are artificially fed prior to the onset of disease. It is assumed that there must be some substrates in formula feed which facilitate gas production in the intestinal flora. Poor systemic and gastrointestinal immunological protection against the bacterial infection in preterm babies predisposes them to infection of the gut. Breast milk appears to be protective for necrotizing enterocolitis.

## CLINICAL FEATURES (FIG. 1)

The age at onset of NEC varies depending on the gestational age of the infant. More immature



**Fig.1:** Clinical features.

preterm infants present later in the hospital course compared to more mature preterm or term infants. NEC in term infants typically presents early, with a reported mean age of onset of 4 days.

The earliest finding often is the intolerance to feeds with vomiting. Vomitus is bile stained in 50% of cases. The first signs of impending disease may be nonspecific, including lethargy and temperature instability, or related to gastrointestinal pathology, such as abdominal distention and gastric retention. Abdominal distension is a common early finding. Abdominal wall erythema and a palpable abdominal mass are common late findings and signify more extensive disease.

The clinical findings of NEC are variable and can involve both abdominal and systemic signs and symptoms. Infants can have rapid changes in findings within a short period of time and require close monitoring for deterioration if NEC is suspected.

Nongastrointestinal signs and symptoms include temperature instability, lethargy, apnea, and bradycardia, while more severe and progressive cases demonstrate instability, of vital signs, respiratory failure, and shock. Gastrointestinal signs and symptoms include poor feeding, increases in pregame residuals, emesis, abdominal distention, and bloody stools. As NEC worsens in severity, gastrointestinal symptoms become more pronounced with marked abdominal distention, gastrointestinal hemorrhage, and abdominal wall discoloration or erythema. Abdominal wall discoloration is often an ominous sign, and a predictor of the severity of NEC.

The differential diagnosis of NEC also requires consideration of spontaneous intestinal perforation, which presents with pneumoperitoneum. This is considered to be a distinct entity from NEC, and occurs earlier in the hospital course than NEC, often in the setting of no or minimal feeding; and is more common among extremely preterm infants (<28 weeks, gestation).

## Signs and Symptoms Associated with Necrotizing Enterocolitis

### Gastrointestinal

- Abdominal distention
- Abdominal tenderness
- Feeding intolerance
- Delayed gastric emptying
- Vomiting
- Occult/gross blood in stool
- Change in stool pattern/diarrhea

### Systemic

- Lethargy
- Apnea/respiratory distress
- Temperature instability
- Acidosis (metabolic and/or respiratory)
- Poor perfusion/shock
- Disseminated intravascular coagulopathy
- Positive results of blood cultures

### ESSENTIAL DIAGNOSTIC POINTS

- Main factors are mucosal injury and formula feeding.
- It is characterized by partial or full thickness intestinal ischemia usually involving the terminal ileum.
- The risk factors include prematurity, neonatal stress, formula feedings, surgery in newborn, umbilical artery catheterization, septicemia and hypoalbuminemia.
- The bacteria responsible for this infection include *E. coli*, *Klebsiella*, *Pseudomonas*, *Salmonella*, and *Clostridium*.
- Stasis of the intestinal contents favors the bacterial overgrowth.
- The earliest finding often is the intolerance to feeds with vomiting.
- Vomitus is bile stained in 50% of cases.
- Abdominal distension is a common early finding.
- Abdominal wall erythema and a palpable abdominal mass are common late findings and signify more extensive disease.

Necrotizing enterocolitis may develop following a red cell transfusion. Bloody stools are seen in 25% of patients. Because of nonspecific signs, sepsis may be suspected before NEC. The spectrum of illness is broad, ranging from mild disease to severe illness with bowel perforation, peritonitis, systemic inflammatory response syndrome, shock, and death. Progression may be rapid, but it is unusual for the disease to progress from mild to severe after 72 hours.

The illness usually develops in one or 2 days. The course may be fulminant with deaths occurring in few hours. Clinical features can be described in three stages:

- *Stage IA*: Unstable temperature, apnea, bradycardia, lethargy, mild abdominal distension and vomiting.
- *Stage IB*: Blood in stools, radiograph shows mild intestinal distension.
- *Stage II*: Bowel sounds are diminished with or without abdominal tenderness. There may be metabolic acidosis, and mild thrombocytopenia. Pneumatosis intestinalis and dilatation of intestines are seen in abdominal radiographs.

- *Stage III:* The infant has low blood pressure, bradycardia, apnea, acidosis, disseminated intravascular coagulation and anuria. There will be frank signs of peritonitis with abdominal tenderness, distension and erythema of abdominal wall, pneumoperitoneum is found in abdominal radiograph.

#### GENERAL FEATURES

- Preterm baby
- Unstable temperature
- Low blood pressure
- Disseminated intravascular coagulation

#### LABORATORY SALIENT FINDINGS

- Blood in stool
- Metabolic acidosis
- Thrombocytopenia
- Pneumatosis intestinalis and dilatation of intestines are seen in abdominal radiographs
- Disseminated intravascular coagulation
- Signs of peritonitis

## DIAGNOSIS

### Radiographic Findings

The primary radiographic finding in NEC is pneumatosis intestinalis, a radiographic appearance of gas within the wall of the small or large intestine. This is the hallmark of NEC and often establishes the diagnosis.

Infants with suspected NEC should have abdominal radiographs taken that include both anteroposterior views and either left-lateral decubitus or cross-table images to evaluate for free intraperitoneal air. Abdominal radiographs should be performed serially until the patient has demonstrated improvement in radiographic findings and clinical symptoms.

Other radiographic findings may include abdominal distention with evidence of ileus, portal venous gas, or pneumoperitoneum. In addition, bowel loops that remain unchanged on serial radiographic films for 24–48 hours raise the concern for ischemic bowel. Infants with evidence of pneumoperitoneum require surgery. The presence of portal venous gas may be associated with a higher eventual need for surgery although its role as a prognostic marker for mortality is unclear.

The diagnostic evaluation of infants with suspected NEC includes evaluation for bloodstream infection, which can accompany NEC and is associated with worse outcome. Urine culture should also be obtained, as a urinary tract infection may precede the diagnosis of NEC.

Patients with NEC should have a complete blood count with differential and serum chemistry monitored. Hematologic changes that occur with NEC include thrombocytopenia, coagulopathy, anemia, neutropenia or neutrophilia, eosinophilia, and lymphopenia; further, the presence of significant hematologic abnormalities is often associated with more severe disease. In addition, infants with NEC may develop hyponatremia, hyperkalemia, and metabolic acidosis. Blood gas measurements should be performed at routine intervals to monitor for acidosis and respiratory deterioration. A lower serum pH (i.e., metabolic acidosis) is associated with advanced disease. If infants appear likely to need surgery or demonstrate Worsening clinical status, coagulation studies should be obtained as disseminated intravascular coagulation is often present in advanced cases of NEC.

## DIFFERENTIAL DIAGNOSIS

- Septicemia
- Meconium plug syndrome
- Malrotation
- Hirschsprung disease

## MANAGEMENT

### Medical Management

There is no definitive treatment for established NEC, so therapy is directed at giving supportive care and preventing further injury with cessation of feeding, nasogastric decompression, and administration of intravenous fluids. Careful attention to respiratory status, coagulation profile, and acid-base and electrolyte balances are important. Once blood has been drawn for culture, systemic antibiotics should be started immediately.

The treatment of NEC is based on the severity and involves bowel decompression, bowel rest, antimicrobial therapy, and monitoring of serial abdominal radiographs and laboratory parameters. Bloodstream infection develops in up to one-third of infants with NEC. Therefore, broad-spectrum antimicrobial therapy is indicated. Most bloodstream infections are caused by gram-negative bacteria, most commonly *Escherichia coli* and *Klebsiella*.

Initial management of the child with necrotizing enterocolitis without pneumoperitoneum is standardized. All oral feedings should be stopped. Nasogastric tube is inserted to relieve distension and aspirate stomach contents. Fluid and electrolyte should be administered. Parenteral intravenous fluid can be used.



Antibiotics must cover gram negative and gram positive aerobic organism. Fungal infection is common after surgical treatment for NEC. Oral nystatin is recommended postoperatively.

### Antibiotic Selection and Duration

There exists wide variation in the choice of antibiotic treatment for NEC, with a combination of vancomycin and gentamicin being the two most commonly used antibiotic agents in this population. Other commonly used antibiotics include ampicillin, cephalosporins, clindamycin, metronidazole, and carbapenems. Randomized controlled trial of 42 infants, the addition of anaerobic coverage with clindamycin to a standard regimen of ampicillin and gentamicin, compared to ampicillin and gentamicin alone, did not reduce the risk of intestinal perforation or death. However, surviving infants in the group receiving clindamycin, compared to ampicillin and gentamicin alone.

The best method of determining which babies require surgery consists of repeated physical examination by the same examiner, flat and left lateral decubitus abdominal radiograph every 4–6 hours for detection of pneumoperitoneum, careful monitoring of respiratory status and acid base balance and monitoring of leucocyte and platelet counts for the signs of sepsis.

Ventilation should be assisted in the presence of apnea or if abdominal distention is contributing to hypoxia and hypercapnia. Intravascular volume replacement with crystalloid or blood products, cardiovascular support with fluid boluses and/or inotropes, and correction of hematologic, metabolic, and electrolyte abnormalities are essential to stabilize the infant with NEC.

The patient's course should be monitored closely by means of physical assessments; sequential anteroposterior and cross lateral or lateral decubitus abdominal radiographs to detect int. perforation; and serial determinations of hematologic, electrolyte acid-base status.

Shock is managed by replacement of fluids and vasopressor agents. Plasma and platelet transfusion are used to prevent bleeding tendency. Surgical intervention is required, if there is perforation.

Free intraperitoneal air is an absolute indication for surgery. However, pneumoperitoneum from the air dissecting down the chest in the ventilator dependent child must be ruled out, so that unnecessary laparotomy is not performed.

Successful medical treatment may be followed by late onset intestinal obstruction as a result of scarring and an intestinal long-term complication is the development of anastomotic ulcer.

### SURGICAL TREATMENT

Indications for surgery include evidence of perforation on abdominal X-ray (pneumoperitoneum) or positive result of abdominal paracentesis (stool or organism on Gram-stain preparation from peritoneal fluid). Failure of medical management, a single fixed bowel loop on radiographs, abdominal wall erythema, and a palpable mass are relative indications for exploratory laparotomy. Ideally, surgery should be performed after intestinal necrosis develops but before perforation and peritonitis occur.

Traditionally, management has involved an exploratory laparotomy with resection of affected bowel. However, especially in infants with a birth weight of less than 1000 g. Peritoneal drainage has become a more commonly used method to provide abdominal decompression until the need for a definitive laparotomy can be reassessed. However, of concern was a higher associated risk of death or neurodevelopmental impairment among infants receiving peritoneal drainage compared to initial laparotomy.

The frankly necrotic or perforated intestine should be removed and ileostomies are formed. When the massive resection is necessary, the chance of the child's survival is limited. But premature infant's intestine still has potential for growth and adaption.

If ileostomy is performed, the mucous fistula should be exteriorized close to functioning ileostomy. Closure should be planned when the child is large enough, i.e., >2 kg and sufficient time after the event, i.e., at least 4–6 weeks to minimize the possibility of recurrence.

The children are not fed orally for at least 2–3 weeks after the onset of NEC, it frequently takes more than 1 month for those successfully treated medically to attain adequate oral caloric intake. Hyperalimentation is mandatory as soon as NEC is diagnosed. Central intravenous alimentation is preferred in NEC.

- *Gastrointestinal perforation:* It is reported among 20–30% of children. It occurs within 10–48 hours after the onset of necrotizing enterocolitis. It is suspected in infants with increasing abdominal distension, an abdominal mass. A serial radiograph suggests persistent fixed loop.



- *Full thickness necrosis of GIT:* These will have the sign of peritonitis. These include ascites, abdominal mass, abdominal wall erythema and induration. Necrosed area is removed surgically.

## Mortality

Cause-specific mortality from NEC is high and varies depending on the gestational age and birth weight of the infant factors associated with a higher risk of death included a lower gestational age, lower birth weight, treatment with assisted ventilation on the day of diagnosis, treatment with vasopressors at the time of diagnosis, and black race. The majority of deaths from NEC occur within 7 days of diagnosis.

## LONG-TERM OUTCOMES

### Neurodevelopmental Impairment

Neurodevelopmental impairment is common among preterm infants with NEC, particularly those infants that required surgery or had a comorbid blood-stream infection. If extremely low birth weight (ELBW) infants with NEC undergo surgery, they are at higher risk for significant long-term cognitive and motor impairment.

Extremely low birth weight infants with sepsis and NEC have a similarly high incidence of neurodevelopmental impairment of 53% compared to an incidence of 29% among ELBW infants without infection. The highest risk of adverse outcomes appears to be in infants with both surgical NEC and late bacteremia, who were found to have 8-fold higher odds of cerebral palsy compared to infants without NEC or late bacteremia.

## PROGNOSIS

Medical management fails in approximately 20–40% of patients with pneumatosis intestinalis at diagnosis; of these, 10–30% die.

Early postoperative complications include wound infection, dehiscence, and stomal problems (prolapse, necrosis). Later complications include intestinal strictures, which develop at the site of the necrotizing lesion is approximately 10% of surgically or medically managed patients. Resection of the obstructing stricture is curative.

After massive intestinal resection, complications from postoperative NEC include short bowel syndrome (malabsorption, growth failure, malnutrition). Complications related to central venous catheters (sepsis, thrombosis) and cholestatic jaundice.

## PREVENTION

Newborns exclusively breastfed have a reduced risk of NEC. Early and aggressive increase in feeding volumes increases the risk of NEC in VLBW infants, although a safe-feeding regimen remains unknown.

Emerging evidence indicates that the use of inhibitors of gastric acid secretion ( $H_2$ -receptor blockers, proton-pump inhibitors) or prolonged empirical antibiotics in early neonatal period is associated with increased risk of NEC. Prophylactic enteral antibiotics reduced the risk of NEC.

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# Tracheoesophageal Fistula

## PRESENTING COMPLAINTS

A 6-month-old boy was brought with the complaints of:

- Cough and cold since birth
- Fever since 1 week

## History of Presenting Complaints

A 6-month-old boy has been referred by a general practitioner for evaluation of repeated respiratory tract infections. His mother revealed history of repeated attacks of cough, cold and fever since birth. Sometimes boy used to have respiratory distress and had been hospitalized a few times. Child was given intravenous antibiotics and intravenous fluids.

## Past History of the Patient

The boy was the only sibling of the family. Boy was born at term by normal vaginal delivery. He cried immediately after birth. Child was having bluish discoloration. Excessive froth was coming from mouth. A nasogastric tube is passed to know the patency of esophagus. But the tube could not

be passed. This helps to make the diagnosis of esophageal atresia. The birth weight was 2.75 kg.

Then pediatric surgeon was consulted. The tracheoesophageal fistula was repaired with satisfactory primary repair. During hospital stay following the period of intravenous feeding, oral feeds were gradually introduced. He was given normal feeds at the time of discharge. But he had cough and noisy breathing. His cough persisted. Despite of all these, he had normal growth and development. The child was on breast milk for first 3 months. Weaning started from 3rd month onwards. Social smile appeared at the age of 3 months. The neck control was present at the age of 3 months. The child was sitting with support at the time of admission.

## EXAMINATION

On examination, the boy was moderately built and moderately nourished. The boy was alert and breathless. Anthropometric measurements included the length was 70 cm (95th centile) and weight was 7 kg (50th centile). The head circumference was 40 cm.

He was febrile. The pulse rate was 128 per minute and the respiratory rate was 60 per minute. Blood pressure recorded was 60/50 mm Hg. There was no pallor, no lymphadenopathy, no edema, and no cyanosis.

Respiratory system revealed presence of rhonchi and crepitations. Wheeze was audible without stethoscope. There was subcostal indrawing and accessory muscles were active. Cardiovascular system revealed tachycardia. Per abdomen examination was normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 7,800 cells/cu mm
DLC	: $P_{55} L_{35} E_7 M_3$
ESR	: 32 mm at 1st hour
AEC	: 660 cells/dL
X-ray chest	: Showed the air outlining the pouch

### CASE AT A GLANCE

#### Basic Findings

Length	: 70 cm (95th centile)
Weight	: 7 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 128 per minute
Respiratory rate	: 60 per minute
Blood pressure	: 60/50 mm Hg

#### Positive Findings

##### History

- Repeated respiratory infections
- Bluish color at birth
- Esophageal atresia (EA)
- Surgical repair done

##### Examination

- Tachypnea
- Rhonchi crepitations
- Audible wheeze

##### Investigation

- X-ray chest: Air outlining the pouch

## DISCUSSION

Esophageal atresia is the most common congenital anomaly of the esophagus, with a prevalence of 1.7 per 10,000 live births. Of these, >90% have an associated tracheoesophageal fistula (TEF). In the most common form of EA, the upper esophagus ends in a blind pouch and the TEF is connected to the distal esophagus. The exact cause is still unknown; associated features include advanced maternal age, obesity, low socioeconomic status, and tobacco smoking.

Anatomic disorders of the esophagus in children can be congenital or acquired. The most common congenital disorder of the esophagus is EA, which can be present with or without a TEF. Other congenital esophageal disorders include esophageal webs, duplications, laryngotracheoesophageal clefts (LTEC), and esophageal stenosis from extrinsic (vascular rings) or intrinsic sources. Acquired disorders of the esophagus include strictures due to foreign body or caustic injury, gastroesophageal reflux, eosinophilic esophagitis, or diverticula.

Infants weighing <1,500 g at birth and those with severe cardiac anomalies have the highest risk for mortality. About 50% of infants are non-syndromic without other anomalies, and the rest have associated anomalies, most often associated with the VATER or VACTERL (vertebral, anorectal, cardiac, tracheal, esophageal, renal, radial, limb) syndrome. Cardiac and vertebral anomalies are seen in 32% and 24%, respectively.

Around day 26 or 27 of gestation, a ventral diverticulum is formed from the caudal end of the primitive pharyngeal foregut. This laryngotracheal diverticulum undergoes elongation and differentiation and eventually forms the larynx, trachea, bronchi, and lungs. In order to separate the dorsal foregut (future esophagus) from the ventral laryngotracheal diverticulum, longitudinal tracheoesophageal folds fuse to form a septum that completely separates these structures. The traditional embryologic theory has held that failure of these folds to completely form, or improper timing of their formation, leads to the anomalies of EA and/or TEF. However, investigators have found little evidence to support that lateral folds forming a tracheoesophageal septum occurs at all.

The embryogenesis of the various types of congenital esophageal stenosis is thought to be similar. An esophageal web is considered by some to represent a variant of EA. The web membrane is composed of squamous epithelium on both sides

and often has a small opening which is why it often does not present in the 1st day or day 2 of life. Also, similar to EA-TEF, the embryology of esophageal stenosis secondary to tracheobronchial remnants is hypothesized to be due to disordered separation of the primitive foregut.

Lastly, the pathogenesis of esophageal stenosis due to fibromuscular hypertrophy is also unknown but may be similar to that of congenital pyloric stenosis.

One recent theory suggests initial normal development of the trachea and esophagus followed by fusion of the two structures to various degrees. Another theory postulates that there is arrest of the cranial extension of the tracheoesophageal septum leading to a persistent single tube.

Esophageal atresia is more common among preterm children. Pathogenesis of this condition is defective differentiation of the primitive foregut into trachea and esophagus. The defective growth of endodermal cells leads to atresia.

Upper part of esophagus is developed from retropharyngeal segment and lower part from pregastric segment of the first part of primitive gut. At 4 weeks of gestation the laryngotracheal groove is formed. Two longitudinal furrows develop. This separates the respiratory precordium from the esophagus. Altered cellular growth in this septum produces formation of tracheoesophageal fistula.

In more than 85% of cases, fistula between the trachea and distal esophagus accompanies atresia. Disorders in the formation and movement of the paired cranial and single caudal folds in the primitive foregut explain the variation in atresia and fistula formation.

The condition is associated with cardiovascular abnormalities, duodenal atresia, imperforate anus, urinary tract infection and skeletal abnormalities. Antenatal maternal hydramnios is associated with this anomaly. This is associated with vertebral, anorectal, cardiac, renal, radial and limb abnormalities.

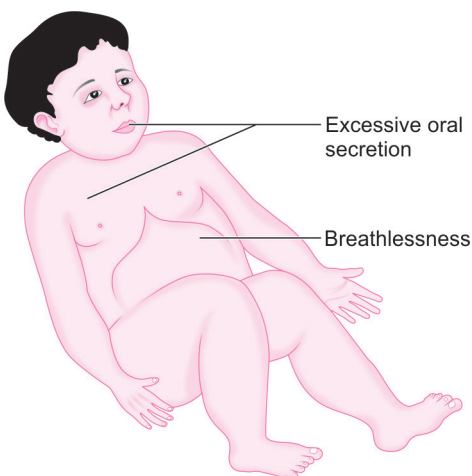
There are five types. In the most common variety the upper part of the esophagus ends blindly. The lower part is connected to the trachea by fistula.

Lack of cartilage in trachea produces variable degree of tracheomalacia. Hence trachea becomes floppy and vulnerable to collapse. Usually there will be secondary problems of this surgical condition. These problems may even be present after successful correction of condition. This is more if there is associated tracheomalacia.

## CLINICAL FEATURES (FIG. 1)

Esophageal atresia and TEF are classified into five different types, and it is useful to use the anatomic description when referring to a specific type. By far the most common anatomic type is EA with distal TEF, in which the fistula most frequently originates just proximal to the carina in the posterior trachea. The second most common type is pure EA with no TEF. The other three types are seen much less frequently and include EA with a proximal TEF, EA with a proximal and distal TEF, and finally, an H-type (or isolated) TEF without EA.

Tracheoesophageal fistula is suspected in the maternal polyhydramnios and in infants with excessive oral secretion. It sometimes presents with the cyanosis choking or coughing in an attempt to feed. Suction of the excessive secretion and pharynx will give temporary relief but symptoms quickly recur. Other signs may be inability to swallow or inability to pass a feeding tube. Respiratory compromise may be seen as well if there is reflux of gastric fluid through the TEF or aspiration from the upper esophagus resulting in a chemical pneumonitis. Acute respiratory failure can be seen when inspired air goes preferentially through the fistula into the gastrointestinal tract, most commonly seen on positive pressure ventilation. In contrast, H-type TEF is often not as clinically apparent in the neonatal period and the diagnosis may be delayed. Thus, a high index of suspicion is required. Clinically, these patients often present with recurrent aspiration pneumonia, a history of coughing or choking with feeds, and cyanotic spells. Aspiration of the gastric contents produces life-threatening clinical pneumonia.



**Fig. 1:** Clinical features.

The neonate typically has frothing and bubbling at the mouth and nose after birth as well as episodes of coughing, cyanosis, and respiratory distress. Feeding exacerbates these symptoms, causes regurgitation, and can precipitate aspiration.

### ESSENTIAL DIAGNOSTIC POINTS

- Cyanosis choking or coughing in an attempt to feed
- Excessive secretion and pharynx
- Associated with vertebral, anorectal, cardiac, renal, radial, and limb abnormalities
- Maternal polyhydramnios
- Abdominal distension
- Recurrent aspiration pneumonia
- Failure to thrive, slow feeding, coughing and choking are common sequelae

If there is a fistula between the trachea and distal esophagus, there will be abdominal distension with tympanic note. Abdominal distension may interfere with breathing. If the fistula is in between trachea and proximal esophagus there will be aspiration pneumonia leading to respiratory distress. If there is fistula without atresia H-type, there will be recurrent aspiration pneumonia, including refractory bronchospasm and recurrent pneumonias. The diagnosis is delayed by days and months.

If the lesion occurs in extrathoracic trachea, obstruction is predominantly inspiratory. The intrathoracic lesions are more to collapse during expiration. These result in noisy breathing. There will be frequent episodes of bronchospasm following the surgeries. This is exaggerated by tracheomalacia.

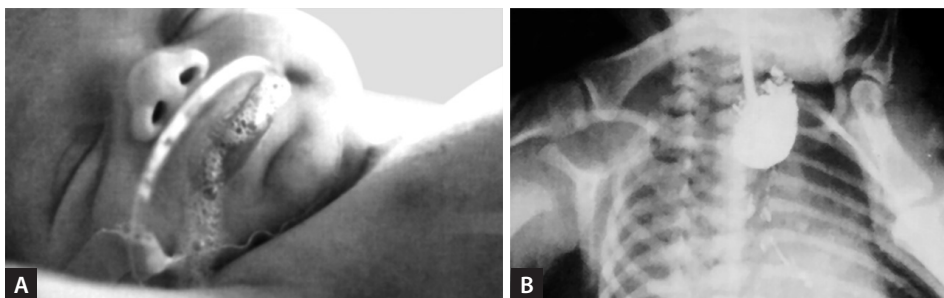
Associated structural malformation such as tracheomalacia, esophageal stenosis should be corrected. Failure to thrive, slow feeding, coughing and choking are common sequelae.

### GENERAL FEATURES

- Excessive oral secretion
- Cyanosis
- Coughing
- Repeated respiratory infection
- Aspiration pneumonia

## DIAGNOSIS

Prenatal diagnosis of EA-TEF is uncommon. A small gastric bubble or polyhydramnios on prenatal ultrasound can be suggestive but is not definitive. Postnatally, the diagnosis of EA with or without TEF is typically made within the 1st day of life. Failure to pass a feeding tube is often the initial



**Figs. 2A and B:** Tracheoesophageal fistula.

step in the diagnosis. Plain chest radiograph can confirm the diagnosis by visualizing the feeding tube in the upper esophageal pouch. The image can be further enhanced by injecting a small amount of air into the feeding tube, which can help highlight the blind upper esophageal pouch consistent with EA. Injecting a very small amount of contrast while under X-ray may be helpful as well in some cases, particularly if trying to differentiate EA from traumatic misplacement of a feeding tube with a pharyngeal or esophageal injury (**Figs. 2A and B**).

The two most common types of EA-TEF can be distinguished on plain chest and abdominal X-rays. With pure EA, there will be no abdominal bowel gas visualized, while EA with distal TEF will have normal abdominal bowel gas pattern. Rigid bronchoscopy is used to confirm the presence of a distal fistula and can also be used to assess for a rare proximal fistula.

The diagnosis of H-type TEF presents a greater challenge. Contrast esophagram, often best performed in prone position, requires a skilled radiologist, as the fistula can be quite difficult to see LERE. Bronchoscopy and esophagoscopy are used, to confirm the diagnosis, though the fistula can still be difficult to visualize.

Over 50% of children with EA-TEF will have other associated anomalies. All neonates with newly diagnosed EA-TEF should be evaluated for other VACTERL-related anomalies. This includes a thorough physical examination, echocardiography, renal ultrasound, spinal ultrasound, and spinal radiographs. Chromosome studies should also be sent.

#### LABORATORY SALIENT FINDINGS

- Inability to pass the catheter into the stomach
- Plain X-ray of the chest shows the upper esophageal pouch dilated with air
- Bronchoscopy detects orifice of the fistula

## DIFFERENTIAL DIAGNOSIS

- Traumatic postintubation
- Gastroesophageal reflux
- Hiatus hernia
- Achalasia

## COMPLICATIONS

The main complication of the tracheoesophageal fistula includes that of respiratory distress and ultimately congestive cardiac failure.

## TREATMENT

### Initial Management

It is a surgical emergency. Preoperatively baby should be kept prone. This is to decrease the aspiration of the gastric content. Esophageal pouch should be kept empty by constant suctioning to prevent aspiration. Temperature and respiratory function are to be monitored.

Gastrostomy for feeding and surgical repair should be undertaken as early as possible. Oral feeding is started 8–10 days after the primary anastomoses. Esophagography done at 10 days will help to determine the adequacy of anastomoses. Stenosis at anastomy is common. This may require dilatation.

Initially, maintaining a patent airway, preoperative proximal pouch decompression to prevent aspiration of secretions and use of antibiotics prevent consequent pneumonia are paramount. Prone positioning minimizes movement of gastric secretions into a distal fistula, and esophageal suctioning minimizes aspiration from a blind pouch. Endotracheal intubation with mechanical ventilation is to be avoided if possible because it can worsen distention of abdominal viscera.

Temporary treatments to help improve ventilation prior to urgent surgical intervention include right mainstem bronchus intubation and



high-frequency oscillatory ventilation. However, intubation may worsen respiratory function because the positive pressure may increase air-flow preferentially through the fistula. Emergent surgical management of worsening respiratory failure in these patients includes decompressive gastrostomy and ligation of the TEF. In those cases, complete repair of the EA may need to be delayed.

Timing of surgical repair depends primarily on the presence and severity or other anomalies or medical conditions.

Surgical ligation of the TEF and primary end-to-end anastomosis of the esophagus via right-sided thoracotomy constitute the current standard surgical approach. In the premature or otherwise complicated infant, a primary closure may be delayed by temporizing with fistula ligation and gastrostomy tube placement. If the gap between the atretic ends of the esophagus is >3–4 cm, primary repair cannot be done; options include using gastric, jejunal, or colonic segments interposed as a neoesophagus. These patients frequently require multiple surgical procedures to bring the two ends of the esophagus together. A gastrostomy is placed early in their management to provide access for enteral feeding and to provide access to the distal esophagus. In some cases, the two ends of the esophagus are never able to be surgically brought together. These patients are candidates for esophageal replacement surgery. Conduits frequently used include the stomach or colonic interposition grafts. Careful search must be undertaken for the common associated cardiac and other anomalies. Thoracoscopic surgical repair is now considered feasible and associated with favorable long-term outcomes.

### Postoperative Care and Complications

Early postoperative complications following repair of EA with or without TEF include anastomotic leak, anastomotic stricture, and recurrent fistula.

Often, an esophagram will be performed between postoperative days 5 and 7 to rule out a leak prior to initiating feeds. Anastomotic leaks occur in 15–20% of patients, with a majority being managed nonoperatively by providing parenteral nutrition and antibiotics until spontaneous closure is documented by a repeat esophagram. After this, oral feedings are begun. Major leaks are rare and usually present with tachypnea, sepsis, and/or tension pneumothorax on the second or third postoperative day. Treatment includes tube thoracostomy and possible re-exploration to control the leak and manage the sepsis.

### PROGNOSIS

Prognosis depends upon the earlier diagnosis, size and maturity of the baby, associated congenital abnormalities and the presence of pneumonitis.

The majority of children with EA and TEF grow up to lead normal complications are often challenging, particularly during the later part of life. Complications of surgery include anastomotic leak, regurgitation and anastomotic stricture.

Gastroesophageal reflux disease contributes significantly to the respiratory disease (reactive airway disease) that often complicates EA and TEF and also worsens the frequent anastomotic strictures after repair of EA. Many patients have an associated tracheomalacia that improves as the child grows.

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# Wilson's Disease

## PRESENTING COMPLAINTS

A 10-year-old girl was brought with the complaints of:

- Yellowish color of eye since 1 month
- Altered speech since 1 month
- Altered walking since 15 days

## History of Presenting Complaints

A 10-year-old girl presented with the history of deterioration of speech and gait since 1 month. Mother noticed that there was some alteration in speech. She was able to understand all that was told. She was answering the questions after repeated hearing. Mother had also noticed change in the walking style. She was assuming hunched posture. She was walking in short jerky steps. Jaundice was present.

### CASE AT A GLANCE

#### Basic Findings

Height	: 132 cm (50th centile)
Weight	: 28 kg (70th centile)
Temperature	: 38°C
Pulse rate	: 96 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 90/70 mm Hg

#### Positive Findings

##### History

- Speech disturbance
- Gait disturbance

##### Examination

- Fine tremors
- Hunched posture
- Icterus
- KF ring
- Hepatomegaly

##### Investigation

- Hemoglobin: 10 g/dL
- Serum bilirubin: Raised
- Serum ceruloplasmin: Decreased
- SGOT, SGPT: Raised
- Serum copper: Increased

(SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase)

## Past History of the Patient

She was elder sibling of consanguineous marriage. She was born at term by normal vaginal delivery. She cried immediately after the delivery. She had normal physiological jaundice at birth. She was exclusively on breast milk for 6 months. Later weaning started. The child had been immunized completely. All the developmental milestones were normal. There was no significant past history apart from common cold.

## EXAMINATION

The child was moderately built and nourished. The girl was looking pale. She was shy with hunched-up posture. Anthropometric measurements included the height 132 cm (50th centile), and the weight was 28 kg (70th centile).

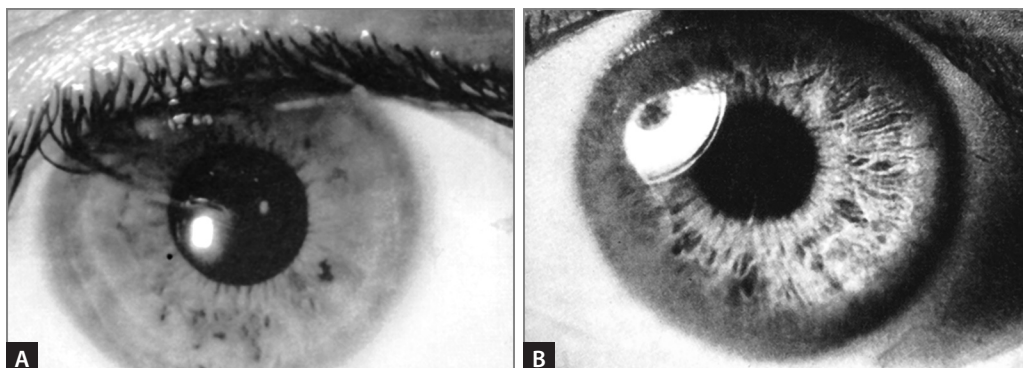
Child was febrile. Pulse rate was 96 per minute and the respiratory rate was 20 per minute. The blood pressure recorded was 90/70 mm Hg. There was no pallor, no lymphadenopathy, and no edema. Icterus was present and Kayser-Fleischer (KF) ring was seen (**Figs. 1A and B**).

Per abdomen examination revealed the presence of enlarged liver. Hepatomegaly was measuring about 4 cm below the costal margin, firm and nontender. There was no splenomegaly and no free fluid in the abdomen.

Higher mental function appeared normal except for speech. There was no cranial nerve involvement. The child had fine tremors when she was asked to show the hands. Deep tendon reflexes were normal. No sensory disturbances were present. Cardiovascular and respiratory systems were normal.

## INVESTIGATION

Hemoglobin	: 10 g/dL
TLC	: 12,300 cells/cu mm
Platelet count	: 200,000 cells/dL
Alkaline phosphatase	: 150 U/L (100–550 U/L)
Serum ceruloplasmin	: 8 mg/dL



**Figs. 1A and B:** Kayser–Fleischer (KF) ring.  
(For color version see Plate 1)

Serum copper	: 1000 µg/dL
Serumbilirubin	: 5 mg/dL
SGPT	: 1000 U/L (Normal range: 6–50 U/L)
SGOT	: 65 U/L (Normal range: 15–55 U/L)
Urine 24-hour copper excretion	: 1000 mg/dL

## DISCUSSION

The neurological symptoms and signs are suggestive of problems associated with the basal ganglia. Hypoalbuminemia along with abnormal liver function tests suggest Wilson's disease. It is also called hepatolenticular degeneration. It is an autosomal recessive disorder characterized by degenerative changes in the brain, liver and KF ring in cornea.

## PATHOGENESIS

The gene locus for Wilson's disease is on the long arm of chromosome 13 and 14q 21. The disease associated gene (ATP 7B) encodes a copper-transporting P-type ATPase, the WND protein. It is likely that there are numerous mutations of the gene, and most patients have twodifferent mutations, having acquired one from each parent. The two most frequently observed mutations are a point mutation resulting in C to A transversion or a frame-shift.

Studies using the recently cloned ceruloplasmin gene indicates that the underlying abnormally is a defect in both translation and transcription of the ceruloplasmin mRNA.

Mutations that completely destroy gene function associated with onset of the disease symptoms as early as 2–3 years of age.

Fetal and neonatal liver normally contains high concentration of sulfur rich copper-binding protein, i.e., metallothionein. Serum ceruloplasmin and serum copper levels are low. Altered incorporation of copper into hepatic proteins such as ceruloplasmin is associated with diffuse accumulation of copper in cytosol of hepatocytes. Later it is deposited in other tissues, for them it is toxic.

With time, liver cells become overloaded and copper is redistributed to other tissues, including the brain and kidneys, causing toxicity, primarily as a potent inhibitor of enzymatic processes. Ionic copper inhibits pyruvate oxidase in brain and ATPase in membranes, leading to decreased adenosine triphosphate-phosphocreatine and potassium content of tissue.

In Wilson's disease, there is no increase in copper absorption from the GI tract. The basic defect seems to be the inability of the liver to incorporate copper into apo-ceruloplasmin, as well as secrete copper into the bile. It has been shown that in patients with Wilson's disease, copper concentrations are very high in the lysosomes of the hepatocytes and very low in the bile.

Copper is an essential trace element and the main dietary sources include liver, shellfish, chocolate, peas, and unprocessed wheat. Normally, 50% of the ingested copper is unabsorbed and 30% is retained by the body for maintaining homeostasis.

Copper accumulated in the hepatocytes induces cell damage through reactive oxygen radicals. Release of copper from necrotic hepatocytes leads to damage of other tissues including the brain, kidneys, and red blood cells. The role of ceruloplasmin, an alpha-2 globulin produced exclusively by the liver, in the pathogenesis of Wilson's disease is unclear. In most patients with Wilson's disease, ceruloplasmin levels are low in the serum.

Altered incorporation of copper into the hepatic proteins such as ceruloplasmin is associated with diffuse accumulation in cytosol of hepatocytes. Copper inhibits pyruvate oxidase in brain and ATPase in the membrane. This leads to decreased ATP, phosphocreatine and potassium content of tissue.

Characteristic histological findings are present in the liver, but none can be considered pathognomonic. The pathologic effects on the liver are considered to be directly related to the accumulation of copper ions. Fat deposition is the earliest change seen. Fine lipid droplets of triglycerides are dispersed throughout the cytoplasm.

In the early precirrhotic stage, the changes resemble a chronic active hepatitis are focal necrosis, scattered acidophilic bodies and moderate to severe steatosis. Glycogenated nuclei in periportal hepatocytes are a typical finding. Kupffer cells are hypertrophied and many contain hemosiderin.

Electron microscopy shows mitochondrial changes. As the hepatic lesion progress collagen deposition occurs, leading on the cirrhosis. In the late cirrhotic stage, periportal fibrosis and portal inflammation is seen along with fibrous bands. The cirrhosis is often macronodular but may be of mixed type also. Cholangiolar proliferation and lymphocytic infiltration is also seen.

All grades of hepatic injury can occur. These include fatty changes, ballooned hepatocytes, glycogen granules, enlarged Kupffer cells and minimal inflammation. These changes are similar to chronic hepatitis. There is large dense mitochondria with altered smooth endoplasmic reticulum.

## **PATHOPHYSIOLOGIC STAGING**

A staging system explains the progression of the disease.

In *stage I*, there is progressive accumulation of copper in the cytosol of hepatocytes. This asymptomatic stage occurs before 5 years and continues until all hepatic binding sites for copper are saturated.

In *stage II*, there is redistribution of copper from the cytosol to the lysosomes of the hepatocytes and simultaneously copper is released from the liver. If the redistribution is rapid, some hepatic cell necrosis occurs and the patient develops features of liver disease. If this redistribution and release occurs slowly, the patient remains asymptomatic.

In *stage III*, lysosomal copper storage progresses leading to stimulation of fibrogenesis and gradual

progression to cirrhosis. Copper accumulation occurs in other tissues such as brain, cornea and kidney during this stage. Rate of copper deposition determines the progression to clinical disease.

In *stage IV*, onset of hepatic or neurologic manifestation occurs.

In *stage V*, irreversible liver or brain damage.

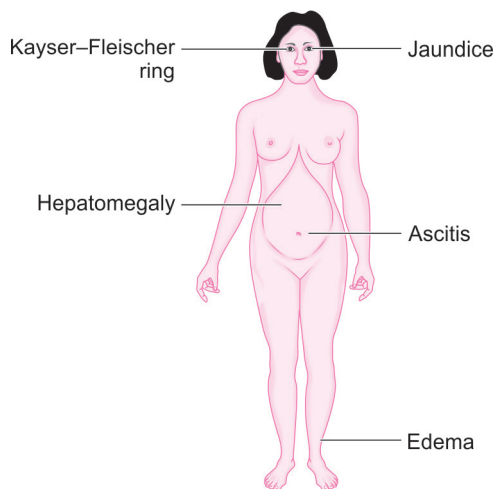
## **CLINICAL FEATURES (FIG. 2)**

The clinical manifestations are related to the deposition of copper in various organs; and rarely presents before 5 years of age. Most patients present with either liver or CNS involvement, even though other organs can also be affected. About 25% of patients have multiple organs involved at presentation. In children, hepatic manifestations usually precede neurologic manifestations by many years.

Wilson trait may be expressed after 2 years of age. Wilson's disease is not seen before 5 years of age.

Copper enters the circulation in the non-ceruloplasmin bound form and accumulates in various organs. The hepatic involvement is more in younger child. Neurological problems are seen in older child. Symptoms are due to the copper induced injury to various organs.

Forms of Wilsonian hepatic disease include asymptomatic hepatomegaly (with or without splenomegaly), subacute or chronic hepatitis, and acute hepatic failure (with or without hemolytic anemia). Cryptogenic cirrhosis, portal hypertension, ascites, edema, variceal bleeding, or other effects of hepatic dysfunction (delayed puberty,



**Fig. 2:** Clinical features.

amenorrhea and coagulation defects) can be manifestations of Wilson's disease.

## Hepatic Disease

The younger the patient, the more likely hepatic involvement will be the predominant manifestation. Girls are three times more likely than boys to present with acute hepatic failure. Clinically evident liver disease may precede neurologic manifestations by as much as 10 years. After 20 years of age, neurologic symptoms predominate.

Many young patients with Wilson's disease present as an acute self limited hepatitis and are often thought to have viral hepatitis. Adolescents usually present with features of chronic active hepatitis. Patients with Wilson's disease may also present as fulminant hepatic failure with rapid progression and death.

Kayser-Fleischer rings are absent in young patients with hepatic Wilson's disease up to 50% of the time but are present in 95% of patients with neurologic symptoms and somewhat over half of those without neurologic symptoms. Psychiatric manifestations include depression, personality changes, anxiety, or psychosis.

Copper diffuses into the cornea from the aqueous humor; and this movement is inversely related to the evaporation of tears from the surface of the cornea. Since evaporation is less at the superior poles of the cornea, KF ring is first visible at the upper part of the limbus.

Sunflower cataracts are occasionally seen in association with KF rings. They appear as a golden disk with radiating spokes, in the anterior capsule of the lens, and will resolve with therapy.

A slit-lamp examination is necessary for detection, even though it can occasionally be visible to the naked eye. The rings are first noted in the upper part, then in the lower part and finally extend laterally to complete the ring. This ring of copper granules deposited in the Descemet's membrane is only a small fraction of the total corneal copper. Most of the copper is deposited in the stromal layers, which does not cause any color change and hence is not visible even under slit lamp.

## Neurologic Disease

Neurologic manifestations typically begin in the second or third decade of life, even though they have been reported to occur as early as 6 years of age. Neurologic disorders can develop insidiously or precipitously, with intention tremor, dysarthria, rigid dystonia, Parkinsonism, choreiform

movements, lack of motor coordination, deterioration in school performance, or behavioral changes, mask-like facies become apparent much later. Intellect is normal.

Central nervous system involvement in Wilson's disease is extensive and not limited to the basal ganglia. Studies have shown that in addition to striatal injury, there is also significant damage to the substantia nigra. However, the damage is limited exclusively to the motor system, with the sensory system being totally spared.

Neurologic disease is almost always associated with the presence of KF rings. KF rings have long been considered the hallmark of Wilson's disease. It is important to remember that they may not be seen in children with only hepatic manifestations of Wilson's disease. In addition, KF rings may also be seen in other conditions, most notably chronic active hepatitis, primary biliary cirrhosis and intra-hepatic cholestatic syndromes. KF rings appear as golden brown or bronze or greenish yellow discoloration (depending on the color of the iris) in the limbic region of the cornea.

Coombs-negative hemolytic anemia may be an initial manifestation, possibly related to the release of large amounts of copper from damaged hepatocytes; this form of Wilson's disease is usually fatal without transplantation. During hemolytic episodes, urinary copper excretion and serum copper levels (non-ceruloplasmin-bound) are markedly elevated. Hemolytic anemia may precede other manifestations and may be self limiting or progress to persistent anemia. The hemolysis occurs due to oxidative injury to the red blood cell membranes from excess serum copper. As a consequence of hemolysis as well as cirrhosis, cholelithiasis may complicate Wilson's disease.

### ESSENTIAL DIAGNOSTIC POINTS

- An autosomal recessive disorder of copper metabolism
- Excessive accumulation of copper in the liver, brain, and kidneys
- The basic defect is inability of the liver to incorporate copper into apo-ceruloplasmin
- *Hepatic disease:* Self-limited hepatitis, chronic active hepatitis, fulminant hepatic failure
- *Central nervous system involvement:* Basal ganglia, striatal injury, substantia nigra
- Tremor, in coordination and difficulty with fine motor functions
- Dysarthria, dystonia, gait disturbances and mask-like facies become apparent much later
- Intellect is normal
- Kayser-Fleischer rings

Electrocardiographic abnormalities have been reported in one-third of patients with Wilson's disease. Bone demineralization is the most common skeletal manifestation.

Renal defects resulting in hypercalciuria and phosphaturia with resultant hypocalcemia and hypophosphatemia are the underlying reason. Renal involvement is common and is characterized by proximal tubular dysfunction and a decrease in glomerular filtration rate.

#### GENERAL FEATURES

- Hepatic failure
- Delayed puberty
- Amenorrhea
- Intention tremor
- Dysarthria
- Dystonia
- Behavioral changes

### DIAGNOSIS

A high index of suspicion is the key to early diagnosis. It is a combination of clinical and family history with a few key investigations that establishes the diagnosis. The classical triad of hepatic disease, neurologic involvement and KF rings represents a late stage in the disease process. About 75% of children presenting with hepatic manifestations of Wilson's disease have decreased ceruloplasmin levels. However, a number of other conditions can also be associated with low serum ceruloplasmin levels.

Wilson's disease should be considered in children and teenagers with unexplained acute or chronic liver disease, neurologic symptoms of unknown cause, acute hemolysis, psychiatric illnesses, behavioral changes, Fanconi syndrome, or unexplained bone (osteoporosis, fractures) or muscle disease (myopathy, arthralgia). The clinical suspicion confirmed by study of indices of copper metabolism.

Most patients with Wilson's disease have decreased ceruloplasmin levels ( $<20$  mg/dL). The failure of copper to be incorporated into ceruloplasmin leads to a plasma protein with a shorter half-life and, therefore, a reduced steady-state concentration of ceruloplasmin in the circulation.

The serum "free" copper level may be elevated in early Wilson's disease ( $>1.6$   $\mu\text{mol/L}$ ), and urinary copper excretion (usually  $<40$   $\mu\text{g/day}$ ) is increased to  $>100$   $\mu\text{g/day}$  and often up to 1,000  $\mu\text{g}$  or more per day (typical findings in Wilson's disease: urine copper excretion  $>1.6$   $\mu\text{mol/24 h}$ ,  $>0.64$   $\mu\text{mol/24 h}$  in children). In equivocal cases, the response of urinary copper output to chelation may be of

diagnostic help. During the 24 hours urine collection patients are given two 500 mg oral doses of D-penicillamine 12 hours apart; affected patients excrete  $>1,600$   $\mu\text{g/24 h}$ .

Demonstration of KF rings, which might not be present in younger children, requires a slit-lamp examination by an ophthalmologist. After adequate treatment, KF rings resolve.

Percutaneous liver biopsy should always be performed if there are no contraindications.

Liver biopsy is of value for determining the extent and severity of liver disease and for measuring the hepatic copper content (normally  $<10$   $\mu\text{g/g}$  dry weight) but is only required if clinical signs and noninvasive tests do not allow a final diagnosis or if another liver disorder is suspected. Hepatic copper accumulation is the hallmark of Wilson's disease and measurement of hepatic parenchymal copper concentration is the method of choice for diagnosis. In Wilson's disease, hepatic copper content usually exceeds 250  $\mu\text{g/g}$  dry weight ( $>4$   $\mu\text{mol/g}$  dry weight is the best biochemical evidence for Wilson's disease but lowering the threshold to 1.2  $\mu\text{mol/g}$  dry weight improves sensitivity without significantly effecting specificity).

#### CONDITIONS ASSOCIATED WITH LOW SERUM CERULOPLASMIN

- Malnutrition
- Protein losing enteropathy
- Acute hepatic failure
- Nephrotic syndrome
- Hereditary hypoceruloplasminemia

Urinary copper levels may be used as a good indicator of response to therapy in Wilson's disease. 24 hours urinary copper levels greater than 1,000  $\mu\text{g}$  after challenge with penicillamine in doses of 750 mg/m<sup>2</sup> body surface are per day in two divided doses is considered by many as diagnostic of Wilson's disease.

#### CONDITIONS ASSOCIATED WITH INCREASED URINARY COPPER LEVELS

- Fulminant hepatic failure
- Chronic active hepatitis
- Primary biliary cirrhosis
- Cholestatic syndrome of infancy

In those, in whom liver biopsy is contraindicated, radioactive copper studies are useful. Incorporation of radiocopper into ceruloplasmin is defective in Wilson's disease. Hence the secondary rise in serum radiocopper levels, which normally occurs at 24–48 hours after an oral load of



the isotope, is not present in patients with Wilson's disease.  $^{65}\text{Cu}$  is a stable and safe copper isotope and is currently recommended for this study.

All asymptomatic relatives especially siblings should be screened, using slit-lamp examination, and measurement of serum ceruloplasmin level and 24 hours urine copper.

Imaging studies of the brain may be helpful in diagnosis. CT scan abnormalities include ventricular dilatation, cortical atrophy, basal ganglia hypodensity, and posterior fossa atrophy.

Ophthalmic involvement results in KF ring. This is usually not seen before the age of 7 years. Screening tests for the family member includes serum ceruloplasmin level, urinary copper excretion and sometimes liver biopsy.

#### LABORATORY SALIENT FINDINGS

- Low serum ceruloplasmin levels
- 24 hours urinary copper levels greater than 1000  $\mu\text{g}$
- Percutaneous liver biopsy
- CT scan abnormalities include ventricular dilatation, cortical atrophy, basal ganglia hypodensity, and posterior fossa atrophy

#### DIFFERENTIAL DIAGNOSIS

- Hepatitis
- Hepatic encephalopathy
- Indian childhood cirrhosis
- Hepatic copper overload syndrome
- Antitrypsin deficiency

#### COMPLICATIONS

- Copper-induced hemolysis
- Arthritis
- Renal failure
- Fanconi syndrome
- Renal tubular acidosis

#### TREATMENT

Treatment includes two aspects: (1) Induction therapy is to reduce copper to subtoxic threshold. This takes usually 4–6 months; (2) Maintenance therapy is to maintain a slightly negative copper balance so as to prevent accumulation and toxicity.

Wilson's disease is fatal if untreated, but successful outcome can be achieved with early effective therapy. Treatment is aimed at chelating excess tissue copper for urinary excretion, preventing copper absorption, and rendering tissue copper nontoxic.

Penicillamine is the drug of choice. It is a derivative of penicillin which chelates copper and

enhances urinary excretion. It is administered orally in four divided doses about 30–45 minutes before food. The daily dose is 20 mg/kg body weight in young children and 750 mg/m<sup>2</sup> body surface area in older children given in two divided doses.

Therapy should be initiated with small doses, and then gradually increased. Pyridoxine supplementation (25 mg thrice weekly) is recommended to offset the anti-pyridoxine effect of penicillamine. There is a dramatic increase in urinary copper excretion, about 48 hours after therapy is begun and values up to 100 times normal may be obtained. Biochemical improvement is slow and may take many months. Improvement in clinical symptoms may, however, be seen within a few weeks of therapy.

In response to chelation, urinary copper excretion markedly increases, and with continued administration, urinary copper levels can become normal, with marked improvement in hepatic and neurologic function and the disappearance of KF rings.

Adequacy of therapy may be assessed by serial determination of 24 hours urinary copper excretion. Calculated free serum copper has also been recommended. Values less than 20 indicate adequate therapy.

Approximately 20% of patients develop significant side effects with penicillamine therapy. These include fever, skin rash, granulocytopenia or thrombocytopenia and usually occur within 3 weeks of commencing treatment. In such cases penicillamine should be discontinued until the reactions resolve. The drug should then be reintroduced at very low doses under cover of prednisolone (0.5 mg/kg/day) and very gradually increased. Once penicillamine is tolerated, prednisolone is withdrawn.

Approximately 10–50% of patients initially treated with penicillamine for neurologic symptoms have a worsening of their condition.

Trientine (triethylenetetramine dihydrochloride) is the alternate chelating agent in patients who do not tolerate penicillamine. Triethylenetetramine dihydrochloride is a preferred alternative, and is considered first-line therapy for some patients. Trientine has few known side effects. Ammonium tetrathiomolybdate is another alternative chelating agent under investigation for patients with neurologic disease; initial results suggest that significantly fewer patients experience neurologic deterioration with this drug compared to penicillamine. It is given 1 hour before food and the dose

is 20 mg/kg/day in children below 10 years of age. Older children and adults require 1.0–1.5 g daily in divided doses. Drug toxicity includes bone marrow suppression, nephrotoxicity, skin and mucosal lesions and iron deficiency anemia. The initial dose is 120 mg/day (20 mg between meals tid and 20 mg with meals tid). Side effects include anemia, leukopenia, thrombocytopenia, and mild elevations of transaminases. Because of its extensive decoppering effect, ammonium tetrathiomolybdate also has antiangiogenic effects.

Elemental zinc (zinc acetate 50 mg thrice daily), an antagonist of copper absorption is another alternative. Copper is absorbed in the proximal small intestine, and once it crosses the intestinal brush border, it binds to and saturates the metallothionein inside the electrolytes.

Zinc has also been used as adjuvant therapy, maintenance therapy or primary therapy in pre-symptomatic patients, owing to its unique ability to impair the gastrointestinal absorption of copper. Zinc acetate is given in adults at a dose of 25–50 mg of elemental zinc three times a day and 25 mg three times a day in children older than 5 years of age. Zinc induces metallothionein synthesis in the enterocytes. Metallothionein bound copper cannot move out of the cells to reach the blood stream. The intestinal cells therefore become loaded with this complexed copper and are then eliminated by desquamation into the intestinal lumen.

Zinc must not be given with penicillamine or trientine, since it chelates with these drugs and forms complexes that are therapeutically inactive. However, zinc acts very slowly and may take months for therapeutic benefit.

Orthotopic liver transplantation (OLT) is indicated only in the following situations: (1) fulminant hepatic failure, (2) severe hepatic decompensation and cirrhosis, with no improvement after 2–3 months of chelation therapy, and (3) severe progressive hepatic insufficiency in a patient who discontinued

treatment. OLT has also been performed for neurological manifestations of Wilson's disease, which was unresponsive to chelation therapy.

A major attempt should be made to restrict dietary copper intake to <1 mg/day. Treatment needs to be life-long once diagnosis has been made.

## PROGNOSIS

Wilson's disease is progressive and fatal if untreated. Among children who present as chronic active hepatitis, almost 50% respond to treatment. Fulminant hepatitis is frequently fatal despite chelation therapy. Patients who present with acute hepatitis or are asymptomatic do very well with treatment.

Prognosis is poor in the acute neurological form of Wilson's disease. Among patients with gradual neurological involvement, 75% respond to treatment.

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## PRESENTING COMPLAINTS

A 13-year-old boy was brought with the complaints of:

- Accident 3 days back
- Swelling of the joint since 2 days
- Restricted movement since 1 day

## History of Presenting Complaints

A 13-year-old boy presented with history of accident in the road. There was injury to left knee. Slowly there was swelling of the joint. This leads to the restricted movement of the joint at knee. Mother revealed significant past history of development of swollen tender left elbow. This has also occurred after the accidental slipping.

## Past History of the Patient

He was the elder sibling of nonconsanguineous marriage. He was born at full term by normal delivery. Baby cried immediately after the delivery. The birth weight was 2.9 kg, length was 49 cm,

and the head circumference was 34 cm. He was exclusively on breast milk for 4 months. His developmental milestones were normal. He was immunized completely. His performance at school was good.

## EXAMINATION

The boy was moderately built and nourished. He was dull and anxious. He was cooperative at the time of examination. His anthropometric measurements included height 140 cm (<50th centile), weight 38 kg (50th centile). He was short.

The child was afebrile, the pulse rate was 96 per minute, and the respiratory rate was 20 per minute. The blood pressure recorded was 110/70 mm Hg. There was pallor, no lymphadenopathy, and no cyanosis.

Knee joint on the left side was swollen, warm, and tender. All the systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 9.7 g/dL
TLC	: 9,900 cells/cu mm
Platelet count	: 400,000 cells/cu mm
PT	: 12 seconds
Active PT	: 40 seconds, i.e., prolonged (Normal: 25–30 seconds)
Clotting factor VIII	: 5% (Normal)
Peripheral blood smear	: Normal
von Willebrand factor	: Normal
X-ray of the knee	: Joint dilated supra- patellar and popliteal bursae. Epiphyseal center of the tibia and femur are enlarged

## DISCUSSION

There is a history of easy bruising, joint swelling after the minor injury. This is associated with the prolonged prothrombin time (PT) and

### CASE AT A GLANCE

#### Basic Findings

Height	: 140 cm (<50th centile)
Weight	: 38 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 96 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 110/70 mm Hg

#### Positive Findings

##### History

- Accident
- Restricted movement at left knee
- Swelling of the left knee

##### Examination

- Swollen tender knee
- Pallor

##### Investigation

- Anemia
- Clotting factor VIII: Decreased
- Active PT: Prolonged
- von Willebrand factor: Negative

partial thromboplastin time (PTT) and reduced level factor VII. This condition is called hemophilia A. It is a classical X-linked recessive condition. In hemophilia A, factor VIII is present, but its clotting function is defective.

The hemophilias are rare inherited bleeding disorders caused by a deficiency or an absence of coagulation factors, usually factors VIII or X. Hemophilia A or classical hemophilia is caused by mutations in the factor VIII (FVIII) gene (*F8*); hemophilia B, also known as Christmas disease, is caused by mutations in the factor IX (FIX) gene (*F9*). The clinical hallmark of the hemophilias is soft tissue and musculoskeletal bleeding that may lead to debilitating arthropathy if untreated.

Hemophilia A and B are caused by mutations in the genes encoding for FVIII and FIX, respectively, which are located in the long arm of chromosome X. The genetic mutations can cause a quantitative reduction in protein expression or a qualitative decrease in protein activity, or both. Insertions, deletions, nonsense, and splice site mutations also are observed. Patients with hemophilia B can have a variety of mutations in the *F9* gene, but missense mutations are the most common.

## ETIOLOGY

It is due to the congenital deficiency of the plasma coagulation factor VIII—*hemophilia A* or factor IX—*hemophilia B*.

Factors VIII and IX participate in a complex required for the activation of factor X. Together with phospholipids and calcium, they form the “tenase,” or factor X-activating, complex. Factor X being activated by either the complex of factors VIII and IX or the complex of tissue factor and factor VII. In vivo, the complex of factor VIIa and tissue factor activates factor IX to initiate clotting. In the laboratory, prothrombin time (PT) measures the activation of factor X by factor VII and is therefore normal in patients with factor VIII or factor IX deficiency.

After injury, the initial hemostatic event is formation of the platelet plug, together with the generation of the fibrin clot that prevents further hemorrhage. In hemophilia A or B, clot formation is delayed and is not robust. Inadequate thrombin generation leads to failure to form a tightly cross-linked fibrin clot to support the platelet plug. Patients with hemophilia slowly form a soft, friable clot. When untreated bleeding occurs in a closed space, such as a joint, cessation of bleeding may be the result of tamponade. With open wounds, in which tamponade cannot occur, profuse bleeding

may result in significant blood loss. The clot that is formed may be friable, and rebleeding occurs during the physiologic lysis of clots or with minimal new trauma.

About 80% of cases of hemophilia are caused by gene carried on X-chromosome that results in a profound depression of the level of the factor VIII, i.e., antihemophilic factor in the plasma. Family history is present in 80%. Since factor VIII does not cross the placenta a bleeding may be evident in the neonatal period. A female carries hemophilia trait but only male offspring suffers from the disease.

Severity of hemophilia is dependent on the level of clotting of factor VIII or IX in blood. The average normal activity of clotting factor in blood is defined as 100%. The activity in an individual determines the clinical severity though the relationship is not strictly parallel. Clotting activity present in 1 mL of pooled plasma is considered as 1 unit.

Severely affected individuals bleed spontaneously into major joints and muscles, and usually have factor level less than 1% (<0.01 IU per mL). Moderately affected hemophiliacs have 1–5% (0.01–0.05 units) factor level and usually bleed only after trauma. Persons mildly affected have 6–24% (0.06–0.24 units) factor level and bleed only as a result of surgery or injury. Normal range of factor level is 50–200% (0.5–2 units).

During pregnancy higher level of factor, over 200% or 2 unit, is seen. The level of activity of the clotting factor remains fairly constant throughout the life of the affected person.

## TYPES OF HEMOPHILIA

In *hemophilia A*, the factor VIII is deficient and in *hemophilia B*, factor IX or Christmas factor. In addition, there are other types of hemophilia that are caused by defect in other clotting factors, such as factors II, V, VII, and X. Von Willebrand disease (vWD) is another more common hereditary disorder.

In patients with vWD, production of Willebrand factors is reduced quantitatively and qualitatively. This disorder affects both males and females equally, and is inherited in autosomal dominant way. The vWD is probably the most common inherited clotting disorder, although it is generally the least severe.

## CLINICAL FEATURES (FIG. 1)

Typically, patients with severe hemophilia can experience spontaneous musculoskeletal bleeding,

while those with mild-to-moderate disease develop bleeding only after significant physical trauma or surgery. However, such spontaneous bleeding is likely induced by the routine trauma of weight-bearing on joints, as patients gain mobility and begin to ambulate late in infancy.

During the newborn period, other common presentations of hemophilia include intracranial hemorrhage and bleeding at phlebotomy, injection, or circumcision. Therefore, infants born of known carrier mothers should not be circumcised until testing for factor VIII or IX has been performed. Older infants and children may experience excessive bruising, hematomas, intracranial bleeding, joint bleeding, muscle bleeding, or mouth bleeding after trauma. Female carriers of hemophilia can experience menorrhagia, other mucocutaneous bleeding, and surgical and trauma-related bleeding.

Clinically, it is not possible to differentiate hemophilia A from hemophilia B. Hemophilia should be suspected in any male child with recurrent episode of prolonged bleeding, occurring spontaneously or following injury or during surgical procedures. A positive family history suggests the possibility of inherited bleeding disorder.

Patients with mild hemophilia who have factor VIII or IX levels  $>5$  IU/dL usually do not have spontaneous hemorrhages. These individuals may experience prolonged bleeding after dental work, surgery, or injuries from moderate trauma and may not be diagnosed until they are older.

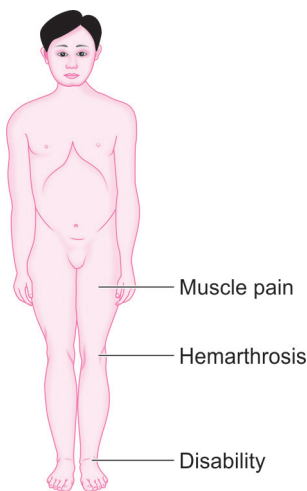
It usually manifests after the 1st year of life with unsightly bruises, prolonged bleeding after

circumcision and minor lesions from mouth. Moderate or mild hemophilia often first appears following surgery, tooth extraction, tonsillectomy, or secondary hemorrhage. Severe hemophiliacs can bleed into confined places—skull, joints, major muscle mass, and this stops only when the pressure around surrounding tissue equals the pressure of escaping blood.

Tongue and mouth laceration is common presentation in toddlers, and occurs due to biting of tongue or lip during fall. Prolonged bleeding after circumcision may be the initial presentation. Gastrointestinal bleeding, genitourinary bleeding and retroperitoneal bleeding are frequent in older children.

Neither factor VIII nor factor IX crosses the placenta; bleeding symptoms may be present from birth or may occur in the fetus. Obvious symptoms such as easy bruising, intramuscular hematomas, and hemarthroses begin when the child begins to cruise. Bleeding from minor traumatic lacerations of the mouth may persist for hours or days and may cause the parents to seek medical evaluation. Although bleeding may occur in any area of the body, the hallmark of hemophilic bleeding is hemarthrosis.

The hallmark of hemophilia is hemarthrosis (**Fig. 2**). Hemorrhages in the elbow, knee and ankles cause pain and swelling. Bleeding into the joints may be induced by minor trauma; many hemarthroses are spontaneous. This will limit the movement of the joint. The earliest joint hemorrhages appear most commonly in the ankle. In the older child and adolescent, hemarthroses of the knees and elbows are also common.



**Fig. 1:** Clinical features.



**Fig. 2:** Hemarthrosis.



Recurrent bleeding may then become spontaneous because of the underlying pathologic changes in the joint. Repeated hemorrhage produces degenerative changes with osteoporosis, muscle atrophy and ultimately fixed unstable joint. Repeated hemarthrosis develops ankylosis, synovial thickening and atrophy of the surrounding muscles. Children with chronic arthropathy are at higher risk of developing joint bleeding.

Although most muscular hemorrhages are clinically evident owing to localized pain or swelling, bleeding into the iliopsoas muscle requires specific mention. A patient may lose large volumes of blood into the iliopsoas muscle, verging on hypovolemic shock, with only a vague area of referred pain in the groin. The hip is held in a flexed, internally rotated position owing to irritation of the iliopsoas. The diagnosis is made clinically from the inability to extend the hip but must be confirmed with ultrasonography or computed tomography (CT) scan. Life-threatening bleeding in the patient with hemophilia is caused by bleeding into vital structures (central nervous system, upper airway) or by exsanguination (external trauma, gastrointestinal or iliopsoas hemorrhage). Prompt treatment with clotting factor concentrate for these life-threatening hemorrhages is imperative. If head trauma is of sufficient concern to suggest radiologic evaluation, factor replacement should precede radiologic evaluation.

Bleeding in the muscle causes severe pain and disability. Children with retroperitoneal bleed may present with severe abdominal pain, anemia and even shock. Intracranial bleed is uncommon. But it is major cause of death. It may be extradural, subdural, and intracerebral. CT scan is essential to confirm the bleed.

#### ESSENTIAL DIAGNOSTIC POINTS

- Easy bruising, joint swelling after the minor injury
- Prolonged PT and PTT, and reduced level factor VII
- Severity of hemophilia is dependent on the level of clotting of factor VIII or IX in blood
- Joint and muscle hemorrhages
- *Types of bleeding:* Gastrointestinal, genitourinary, retroperitoneal, and intracranial bleeding
- CT scan helps to confirm bleed

An individual with hemophilia B bleeds less frequently. Irritability, guarding tingling and numbness, and limitation of movement of affected joints are early symptoms. Knee and elbow joints are most frequently affected. However, any weight-bearing joint can be affected. The joints are

swollen, warm, tender, and have limitation of movements.

The leading cause of mortality in hemophiliacs is intracranial bleeding. The incidence is 10–15% and risk of ICH ranges from 2 to 3.5% per year. Acute pain is one of the immediate results of untreated internal bleeding. Repeated bleeding into the same joint eventually leads to damage to joint cartilage and synovium, and results in chronic, painful and incapacitating arthritis.

#### GENERAL FEATURES

- Easy bruising
- Intramuscular hematomas
- Irritability
- Intracranial bleeding
- Guarding

#### DIAGNOSIS

The laboratory screening test that is affected by a reduced level of factor VIII or IX is PTT. Patients with hemophilia have a normal platelet count and PT. However, the activated partial thromboplastin time (aPTT) is usually prolonged. In the event of an elevated aPTT in a patient with bleeding symptoms, a diagnosis of hemophilia must be confirmed by specific clotting factor functional assays. In severe hemophilia, the PTT value is usually two to three times the upper limit of normal. The specific assay for factors VIII and IX will confirm the diagnosis of hemophilia. In patients with hemophilia who receive infusions of factor VIII or IX, a factor-specific antibody may develop. These antibodies are directed against the active clotting site and are termed inhibitors. In such patients, the quantitative Bethesda assay for inhibitors should be performed to measure the antibody titer.

Children will have normal bleeding time with prolonged clotting and PPT. Factor VIII and IX deficiencies are recognized. Correction of aPTT with normal serum but not with adsorbed plasma suggests factor IX deficiency. aPTT correction with adsorbed plasma and not with normal serum suggests factor VIII deficiency. Platelet count is normal or elevated. Anemia is proportional to blood loss.

#### DIFFERENTIAL DIAGNOSIS

- Septic arthritis
- Rheumatic fever
- Idiopathic thrombocytopenic purpura (ITP)
- von Willebrand disease

**LABORATORY SALIENT FINDINGS**

- Normal bleeding time with prolonged clotting and partial thromboplastin time
- Factor VIII and IX deficiencies
- Platelet count is normal or elevated
- Anemia is proportional to blood loss

**MANAGEMENT**

Management of hemophiliac children not only includes control of bleeding with replacement therapy of deficient factor, but also a comprehensive team approach. The comprehensive care of these patients involves team approach of hematologists, physiotherapists, surgeons and orthopedic surgeons experienced in handling hemophiliac patients, dentists, psychologists, medical social workers, etc. It is essential to educate the patient and his family, and concerned people about the disease, steps to prevent bleeding and need to seek early medical care.

The fundamental treatment of bleeding in hemophilia is replacement therapy of missing coagulation factors. Proper and prompt use of conservative and preventive measures will help in the management of bleeding, and preventing further damage to the tissues and organs. Treatment is mainly given to minimize permanent damage, symptomatic relief of the pain, prevention of tissue damage, permit tissue healing and restore the function.

Whenever available factors, such as cryoprecipitate, fresh plasma and specific factor concentrate should be administered as promptly as possible when the bleeding episode begins or is recognized. Even early minimal amount of replacement therapy in conjunction with conservative management and preventive measures helps in the management of bleeding problems in hemophiliac patients particularly in developing countries. However, with the availability of factor concentrates it is now possible for hemophiliacs to live a normal healthy life.

**Prevention of Bleeding**

Conservative management like application of ice wrapped in thick cloth applied at the local site of bleeding and pressure bandage are effective in stopping bleeding.

Local bleeding from the tooth, tongue, gingival, etc., may be stopped by applying topical thrombin preparation or gauge soaked in diluted epinephrine solution (1:10,000 aqueous epinephrine). Topical hemostatic preparation may also be applied to the skin abrasions.

Bleeding in the mouth cavity or gum may be controlled using EACA (75 mg/kg/dose) or tranexamic acid (75 mg/kg/day) mixed with water and kept in mouth or gargled and then swallowed. Hematuria can be treated with watchful waiting and high fluid intake, i.e., 150–200 mL/h to prevent clot genitourinary tract.

In many cases of mild hemophilia A and most cases of vWD, desmopressin is useful as it is capable of releasing sufficient factor VIII, particularly in mild-to-moderate hemophiliac cases. This hormone (DDAVP) can be given intravenously, by subcutaneous injection, or in highly concentrated preparations by intranasal spray.

DDAVP when administered intravenously in dose of 0.3 µg/kg produces 3–5 fold increase in plasma level of factor VIII and von Willebrand factor. Side effects are minimal which include facial flushing, headache, tachycardia, abdominal cramps, nausea, and hypo/hypertension.

Hemarthrosis is managed by 25 units of the factor VII per kg body weight every 12th hourly for 1 day. Aspiration of blood from the joint should not be done. Aspirin or indomethacin cannot be used to reduce the pain as these inhibit platelet functions. Hence, paracetamol, pethidine or diazepam may be used.

Infection predisposes hemophiliacs to further bleeding and hence early antibiotic therapy is recommended during proven infection. However, intramuscular injection should be avoided because of risk of provoking hemorrhage and hematoma.

**Replacement of Deficient Factor to Prevent Hemorrhage**

Replacement of the deficient factor is the mainstay in management of hereditary coagulation disorder. The main aim of replacement therapy is to raise the level of deficient clotting factor to a level which will achieve hemostasis and prompt arrest of the bleeding, and maintain it till complete healing takes place. Therefore before giving the treatment, it is essential to know the exact nature and degree of deficiency of the factor.

One unit of factor VIII or IX is the amount of factor present in 1 cc of fresh, normal citrated plasma prepared from the blood collected in 3.8% trisodium citrate solution in the proportion of 9:1.

Therapeutic materials available for the treatment of classical hemophilia are as follows.

***Fresh Whole Blood***

This is used only when there is acute blood loss or hypovolemia. However, the amount of blood

and the rate of transfusion required to achieve hemostatic level of factor VIII are to be practicable. Factors VIII and V are labile, and hence they disappear from the stored blood.

### *Fresh Frozen Plasma*

Fresh frozen plasma (FFP) became the mainstay of plasma replacement therapy. In this process whole blood is collected in citrate-phosphate-dextrose (CPD) or in CPD adenine, centrifuged within 4–6 hours after collection. The supernatant plasma diluted approximately 20% by anticoagulants, separated in a closed system and stored at or below 30°C.

This plasma contains essentially normal level of factors except factors V and VIII which often lose some activities during several months of storage even at 30°C. Factor VIII level is present normally at 0.6–0.7 U/mL (60–70%). Each bag of FFP contains 180–220 mL of plasma (approximately 180–200 units of factor VIII and IX). It is readily available in the thawed material. It is useful only in the management of mild bleeding. Only 10–15 mL of plasma/kg may be given with safety in a single dose with an expected rise of 20–30% in factor VIII activity. It should be compatible with the recipient's ABO blood type to avoid transfusion reactions.

Plasma transfusion is the only known treatment for patients with rare inherited deficiency of factors V, XI, XII, and XIII. The treatment for hemorrhagic episodes in patients with Christmas disease (factor IX deficiency) is use of plasma, which need not be fresh frozen because factor IX is stable in stored plasma. However, factor concentrate may also be used. It is also useful in acquired bleeding disorders such as DIC and hemorrhages secondary to liver disease.

### *Cryoprecipitate*

One of the most important breakthrough in the management of hemophilia is the development of cryoprecipitate. FFP is collected within 6 hours of procurement of blood and rapidly frozen at 70°C. It is then slowly thawed at 2–4°C for 18–24 hours. Subsequently plasma is separated by rapid centrifugation to form the precipitate which is refrozen and stored at temperature below 18°C for 3–12 months. The supernatant plasma is used for other purposes also as it contains all clotting factors except factor VIII and fibrinogen.

Cryoprecipitate contains: (i) antihemophilic factor (factor VIII); 40–160 U/bag; (ii) ristocetin

factor or von Willebrand factor (factor VIII co-factor); (iii) factor VIII-related antigen (factor VIII Ag); (iv) fibrinogen (200–250 mg of fibrinogen/bag); (v) fibronectin (cold-insoluble globulin); and (vi) factor XIII and trace elements of other factors.

### **Factor VIII Concentrate (Lyophilized Antihemophilic Factor)**

Lyophilized concentrates containing 250–1,500 units of factor VIIIc in a reconstituted volume of about 25 cc and are prepared from large pools of fresh frozen plasma from 2,000 to 5,000 paid donors. Factor VIII is purified by combining cryoprecipitation and precipitation with glycine, polyethylene glycol or ethanol, and further fractionated and freeze-dried.

Early, appropriate therapy is the hallmark or excellent hemophilia care. When mild-to-moderate bleeding occurs, values of factor VIII or IX factor must be raised to hemostatic levels, in the 35–50% range. For life-threatening or major hemorrhages, the dose should aim to achieve of 100% activity.

Dose of the factors hemostatic levels of factor VIII required may vary because of the following:

- Type of bleeding episode
- Infection at the site of bleeding. It increases the dose of factor VIII and the duration of therapy.
- Interference with the wound. It should be minimal. Handling should be appropriately timed, e.g., dressing of the wound and physiotherapy should be done after factor VIII administration.

Calculation of the dose of recombinant factor VIII (rFVIII) or recombinant factor IX (rFIX) is as follows:

- Dose of rFVIII (IU) = % Desired (rise in rFVIII) × Body weight (kg) × 0.5
- Dose of rFIX (IU) = % Desired (rise of plasma rFIX) × Body weight (kg) × 1.4

For factor VIII, the correction factor is based on the volume of distribution of factor VIII. For factor IX, the correction factor is based on the volume of distribution and the observed rise in plasma level after infusion of recombinant factor IX.

With patient severe hemophilia and hemarthrosis requires 15 U/kg of factor VII every 12–24 hours for 1–2 days. In intracranial hemorrhage, 40–50 U/kg every 12 hours for 7–14 days is recommended.

When lyophilized products are used, dosage may be calculated to the nearest vial based on

the assay amount printed on the manufacturer's label. When the bags of cryoprecipitate are used, the calculation should be to the nearest bag and should be calculated based on 100 U/bag as the average content. However, this amount varies from one blood bank to another.

### Prothrombin Complex Concentrates (PCC)

Lyophilized concentrates of factors II, VII, IX, and X containing 500–1,000 IU of factor IX in 25 cc are marketed mainly for treatment of factor IX deficiency. However, they can be used for other rare bleeding disorders as in congenital or acquired deficiencies of factors II, VII, and X. It is also used for the patients with antibodies for factors VII and IX.

### Activated Prothrombin Complex Concentrates (APCC)

This product was mainly developed to bypass factor VIII or IX, especially for persons with high level of inhibitors to factors VII and IX. However, high cost, high risk of transmission of hepatitis and AIDS, and difficulty in laboratory monitoring for the effectiveness have limited its use.

### Porcine Factor VIII Concentrate

Factor VIII concentrate made from porcine plasma has low cross activity towards most antibodies. Use of this product was limited in the past due to severe adverse effects such as anaphylaxis, thrombocytopenia and pyrogenic reactions.

The frequency of administration of the factors mainly depends on the half-life of the involved factors. The half-life of factor VIII is 12 hours and that for factor IX 18–24 hours. Hence factor VIII needs to be infused twice a day and the second dose being at least two-thirds of the former. For Christmas disease, once a day replacement is sufficient.

*Duration of treatment depends on the following factors:*

- Severity of the bleeding
- Site of bleeding
- Extent of the tissue damage and how long the wound remains in fragile state, and
- Time required for wound healing

### For Mild Hemorrhage and Hemarthrosis

The therapy should be continued for 1–2 days or till pain in the joint subsides, for major bleeds 3–7 days, for dental extraction 7–10 days, for

laparotomy 10–14 days; and for deep tissue operation 3–4 weeks. Hence, before embarking on any surgical procedure, it is necessary to ensure that sufficient material is available, patients can afford, and adequate laboratory facilities for investigations required, e.g., aPTT and factors assays, are available to monitor.

### Plasma-borne Infections

Transfusion hepatitis, there are multiple causes of hepatitis-A, B, Non-A, Non-B, C and cytomegalovirus; chronic liver disease (CLD) retrospective reviews it has been shown that most ICH often occurs in patients with platelet counts below  $20 \times 10^9/L$ . When the period of thrombocytopenia is reduced, it reduces the risk of ICH.

## TREATMENT

### Hemarthrosis

*Hemophilia A:* 50–60 IU/kg factor VIII concentrate on day 1; then 20–30 IU/kg on days 2, 3, 5 until joint function is normal or back to baseline. Consider additional treatment every other day for 7–10 days. Consider prophylaxis.

*Hemophilia B:* 80–100 IU/kg on day 1; then 40 IU/kg on 2–4 days. Consider additional treatment every other day for 7–10 days. Consider prophylaxis.

### Muscular or Significant Subcutaneous Hematoma

*Hemophilia A:* 50 IU/kg factor VIII concentrate; 20 IU/kg every other day, treatment may be needed until resolved.

*Hemophilia B:* 80 IU/kg factor IX concentrate; treatment every 2–3 days may be needed until resolved.

### Mouth, Deciduous Tooth, or Tooth Extraction

*Hemophilia A:* 20 IU/kg factor VIII concentrate; antifibrinolytic therapy; remove loose deciduous tooth.

*Hemophilia B:* 40 IU/kg factor IX concentrate; antifibrinolytic therapy; remove loose deciduous tooth.

### Epistaxis

*Hemophilia A:* Apply pressure for 15–20 minutes; pack with petrolatum gauze; give antifibrinolytic therapy; 20 IU/kg factor VIII concentrate, if this treatment fails.

*Hemophilia B:* Apply pressure for 15–20 minutes; pack with petrolatum gauze; give antifibrinolytic therapy; 30 IU/kg factor IX concentrate, if this treatment fails.

## Major Surgery, Life-threatening Hemorrhage

*Hemophilia A:* 50–75 IU/kg factor VIII concentrate, then initiate 25 IU/kg q8–12h to maintain trough level >50 IU/dL for 5–7 days, then 50 IU/kg q24h to maintain trough >25 IU/dL for 7 days.

*Hemophilia B:* 120 IU/kg factor IX concentrate, then 50–60 IU/kg every 12–24 hours to maintain factor IX at >40 IU/dL for 5–7 days, and then at >30 IU/dL for 7 days.

## Hematuria

*Hemophilia A:* Bed rest; 1.5 × maintenance fluids; if not controlled in 1–2 days, 20 IU/kg factor VIII concentrate; if not controlled, give prednisone (unless patient is HIV-infected).

*Hemophilia B:* Bed rest; 1.5 × maintenance fluids; if not controlled in 1–2 days, 40 IU/kg factor IX concentrate; if not controlled, give prednisone (unless patient is HIV-infected).

## Prophylactic Therapy

It includes 10–20 units of factor VIII twice or thrice a week to convert severe hemophilia to moderate one. Drugs such as epsilon-aminocaproic acid (EACA) and tranexamic acid are inhibitors of fibrinolytic enzyme. These inhibit the clot lysis and promote the homeostasis. Desmopressin acetate is useful in stopping bleeding.

*For minor surgery:* Plasma level should be elevated to 100% one hour prior to procedure (50 U/kg) and

maintain the plasma level above 60% for 4 days and above 20% for subsequent 4 days.

*For major surgery:* Initial dose is same as above the level is elevated to 100%, next 4 days factor level is maintained at 60% and subsequent 4 days 40% levels are maintained till all drains and sutures are removed.

*For orthopedic surgery:* Factor level should be maintained to 100%. After the operation plasma factor level should be maintained at 80% with 40 U/kg three times a day for 4 days. 40% level should be maintained for subsequent 4 days.

Antenatal diagnosis is possible for obtaining fetal blood at 18–20 weeks of gestation in male fetuses. Affected factors will have reduced level of procoagulant competent of factor VIII.

*Hemophilia A:* 20–40 IU/kg factor VIII concentrate every other day to achieve a trough level ≥1%.

*Hemophilia B:* 30–50 IU/kg factor IX concentrate every 2–3 days to achieve a trough level ≥1%.

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# Hemorrhagic Disease of the Newborn

## PRESENTING COMPLAINTS

A 3-day-old girl was brought with the complaints of:

- Blood in stool since 1 day
- Blood staining at umbilical cord since 1 day

## History of Presenting Complaints

A 3-day-old girl was brought to the hospital with a history of passing the blood in motion. Her mother told that her child passed meconium for the first 2 days. Later child passed yellowish curdled type of motion two to three times. She noticed that next motion was blood stained and subsequent motions were bloody. Child was not irritable. Mother also complained of blood staining at the umbilical cord.

## Past History of the Patient

The child was born at full term by normal vaginal delivery. Child was delivered at home. The age of the mother at the time of delivery was 17 years.

There was history of mother taking sleeping pills often. The postnatal period was normal. The birth weight of the child was 3.25 kg. The head circumference was 35 cm. The child started taking breastfeeds regularly. There was no history of cracked nipple.

## EXAMINATION

The newborn was moderately built and nourished. There was no dysmorphic features. Features of postdated delivery were present. Anthropometric measurements include the weight was 3 kg (50th centile), the length was 50 cm (50th centile), and the head circumference was 35 cm.

The child was afebrile. The pulse rate was 116 per minute and respiratory rate was 34 per minute. Blood pressure recorded was 56/42 mm Hg. There was no pallor, no cyanosis and significant lymphadenopathy. Bleeding was present at the umbilical stump. Abdominal examination was normal. All other systemic examinations were normal.

## CASE AT A GLANCE

### Basic Findings

Length	: 50 cm (50th centile)
Weight	: 3 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 116 per minute
Respiratory rate	: 34 per minute
Blood pressure	: 56/42 mm Hg

### Positive Findings

#### History

- Blood in motion
- Bleeding at umbilical stump

#### Examination

- Bleeding at umbilical stump
- Normal systemic examinations

#### Investigation

- PT: Increased
- PTT: Increased
- Decreased level of clotting factors

(PT: prothrombin time; PTT: partial thromboplastin time)

## INVESTIGATION

Hemoglobin	: 16.5 g/dL
TLC	: 10,000 cells/cu mm
DLC	: $P_{65}L_{28}E_{6}M_1B_0$
Platelet count	: 400,000 cells/cu mm
PT	: 15 seconds
PTT	: 40 seconds
Clotting factors	: II, VII, IX and X are decreased

## DISCUSSION

The history of ingestion of the sleeping pills could be an important factor, but the platelet count is normal, and hence it may not be thrombocytopenia. Infants with disseminated *Enterovirus* may develop bleeding as a result of bleeding necrosis and disseminated intravascular coagulation (DIC).

There is often a history of maternal peripartum illness. These babies usually present at the age of 3–5 days of life. Here hepatosplenomegaly

is present. Baby is extremely sick. Clotting factor studies would show the defects of intrinsic and extrinsic system and thrombocytopenia. Hemorrhagic disease of the newborn is usually due to vitamin K deficiency.

## INTRODUCTION

Vitamin K deficiency bleeding (VKDB) of the newborn, previously known as hemorrhagic disease of the newborn, is classified as: early, classical, or late.

*Early-onset VKDB* occurs in the first 24 hours of life and is due to the cross-placental transfer of compounds that interfere with vitamin K metabolism or function, including some anticonvulsant drugs, antibiotics, antituberculous agents, and vitamin K antagonists.

*Classical VKDB* occurs in the 1st week of life and is due to a physiological deficiency in vitamin K at birth combined with a lack of vitamin K in breast milk or inadequate feeding. Vitamin K prophylaxis has its biggest impact in preventing this type of bleeding.

*Late-onset VKDB* can occur at any age, although it is classically described as occurring between 2 weeks and 6 months of age. In infants, it is again due to inadequate vitamin K content in breast milk and is thus found almost universally in those exclusively breastfed.

## PATHOGENESIS

Hemorrhagic disease of the newborn resulting from severe transient deficiencies in vitamin K-dependent factors is characterized by bleeding that tends to be gastrointestinal, nasal, subgaleal, intracranial, or post-circumcision. Prodromal or warning signs (mild bleeding) may occur before serious intracranial hemorrhage. The prothrombin time (PT), blood coagulation time, and partial thromboplastin time (PTT) are prolonged, and levels of prothrombin (II) and factors VII, IX, and X are decreased. Vitamin K facilitates post-transcriptional carboxylation of factors II, VII, IX, and X. In the absence of carboxylation, such factors form PIVKA (proteins induced in vitamin K absence), which is a sensitive marker for vitamin K status. Bleeding time, fibrinogen, factors V and VIII, platelets, capillary fragility, and clot retraction are normal for maturity.

A transient deficiency of vitamin K occurs. This is probably due to lack of free vitamin K in mother, immaturity of the liver in infants and absence of bacterial intestinal flora. This is responsible for synthesis of vitamin K. Severe deficiency of

vitamin K-dependent factor has been reported in infants born to a mother receiving anticonvulsants during pregnancy especially phenobarbitone and phenytoin. Transfer of vitamin K from mother to fetus is low so that newborn plasma levels are less than one-tenth of maternal levels. Hence concentration of vitamin-dependent factor will come down in first few weeks of life in solely breastfed babies of inadequate intake.

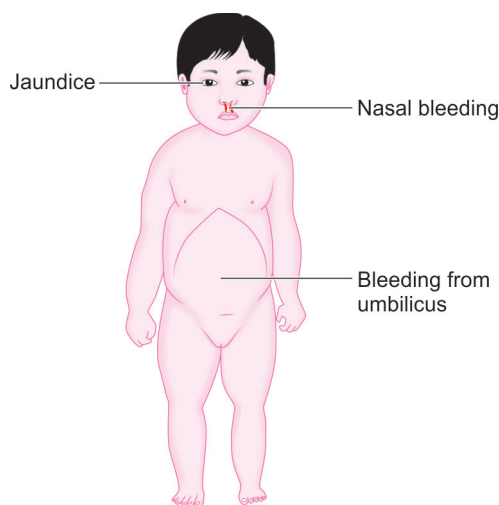
A moderate decrease in factors II, VII, IX, and X normally occurs in all newborn infants by 48–72 hours after birth, with a gradual return to birth levels by 7–10 days of age. This transient deficiency of vitamin K-dependent factors is probably caused by lack of free vitamin K from the mother and absence of the bacterial intestinal flora responsible for the synthesis of vitamin K.

The prolongation of this deficiency is seen in premature infants between 2nd and 5th day of life. This results in moderate decrease in vitamin K-dependent factors. These include clotting factors II, VII, IX, and X. The decrease is normally seen in all newborns by 48–72 hours after birth. They gradually return to normal by 7–10 days. This results in spontaneous and prolonged bleeding. Breast milk is poor source of vitamin K and hence it is more with breastfed infants.

Breast milk is a poor source of vitamin K, but hemorrhagic complications are more frequent in breastfed than in formula-fed infants. This classic form of hemorrhagic disease of the newborn, which is responsive to and prevented by vitamin K therapy, must be distinguished from disseminated intravascular coagulopathy and from the more infrequent congenital deficiencies of one or more of the other factors that are unresponsive to vitamin K. Early-onset life-threatening vitamin K deficiency induced bleeding (onset from birth to 24 hours) also occurs if the mother has been treated with drugs (phenobarbital, phenytoin) that interfere with vitamin K function. Late onset (>2 weeks) is often associated with vitamin K malabsorption, as noted in neonatal hepatitis or biliary atresia.

## CLINICAL FEATURES (FIG. 1)

The clinical features of VKDB are similar to other coagulation disorders. The typical presenting symptoms are bruising mucous membrane bleeding excessive bleeding associated with trauma or invasive procedures, or signs of internal hemorrhage such as abdominal pain, headache, or vomiting. While so-called warning bleeds (bruising, epistaxis) may precede severe internal hemorrhage, they do not always occur. The incidence



**Fig. 1:** Clinical features.

of intracranial hemorrhage in late-onset VKDB is 30–60%. Bleeding in a newborn can be serious. A lot of blood can be lost in few minutes from the umbilical stump and also because the intracranial hemorrhage may also occur.

#### ESSENTIAL DIAGNOSTIC POINTS

- History of maternal peripartum illness
- Babies usually present at the age of 3–5 days of life
- Hepatosplenomegaly is present
- Clotting factor studies would show the defects of intrinsic and extrinsic system
- Thrombocytopenia
- Usually due to vitamin K deficiency
- Moderate decrease of clotting factors II, VII, IX, and X

### DIAGNOSIS

There will be bleeding in gastrointestinal tract, nasal bleeding and intracranial hemorrhage. Bleeding time (BT), clotting time (CT), PTT are prolonged. Clotting factors II, VII, IX, and X are reduced. BT, fibrinogen, factor V and VII, platelets, capillary fragility, and clot retraction or normal for maturity. However, severe bleeding in premature infants may require blood transfusion.

Essential investigations for all cases include hemoglobin (Hb) estimation, red cell morphology, total leukocyte count, differential leukocyte count, platelet count, and reticulocyte count.

#### Apt Test

This test should be performed when there is only gastrointestinal bleeding in a well neonate in the first 48 hours of life and is used to distinguish maternal from neonatal blood. One part of

vomitus is mixed with five parts of distilled water and centrifuged. To the pink centrifuged supernatant fluid, 1 mL of 1% sodium hydroxide is added and wait for 1–2 minutes, if the solution changes to yellow brown color, it favors possibility of swallowed maternal blood (HbA gets denatured by alkali while HbF stays pink).

### Screening Tests

Patients suspected of having VKDB should have a complete blood count (CBC) to assess the platelet count, and PT and activated partial thromboplastin time (aPTT) tests to screen for deficiencies of specific clotting factors. The PT is always prolonged, often to a very significant degree, and the aPTT is usually increased as well. In early or mild vitamin K deficiency, it is possible that only factor VII is reduced, due to its short half-life, thus leading to a prolonged PT but normal aPTT. In the typical scenario, the PT is prolonged out of proportion to the aPTT, e.g., the PT being about four times the mean of the normal range versus an aPTT, i.e., approximately twice normal.

A neonate who has a positive bleeding history or is having active bleeding should have a platelet count, BT, PTT, and PT done. If the results are normal, a thrombin time and von Willebrand factor testing should be considered. If the initial test results are abnormal, special tests should be planned.

### Special Tests

Special tests are required to: (1) Identify the deficient coagulation factor; (2) To determine the degree of deficiency; and (3) To detect and quantitate immune inhibitors. They include prothrombin consumption test, coagulation factor assays and platelet function tests.

#### GENERAL FEATURES

- Gastrointestinal bleeding
- Melena
- Hematemesis
- Not taking feeds

#### LABORATORY SALIENT FINDINGS

- BT, CT, and PTT are prolonged
- Clotting factors II, VII, IX, and X are reduced

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes hemophilia and other congenital factor deficiencies, von Willebrand disease, platelet function abnormalities, and

liver disease-associated coagulopathy. The most common disorder that can be mistaken for VKDB is liver disease-associated coagulopathy, as both results from deficiencies of some of the same clotting factors. The vitamin K-dependent factors II, VII, IX, and X are all synthesized in the liver and are deficient in both conditions. Thus, the PT, aPTT, and specific measurement of these factors will not distinguish the two conditions. Moreover, the two conditions can coexist as liver dysfunction resulting from obstructed biliary flow, which can lead to vitamin K deficiency. Ultimately, the lack of response to parenteral vitamin K administration may be the most important diagnostic clue.

## TREATMENT

Intramuscular administration of 1 mg of vitamin K at the time of birth prevents the decrease in vitamin K-dependent factors in full-term infants, but it is not uniformly effective in the prophylaxis of hemorrhagic disease of the newborn, particularly in breastfed and is premature infants. The disease may be effectively treated with a slow intravenous infusion of 1–5 mg of vitamin K, with improvement coagulation defects and cessation of bleeding noted within a few hours. Serious bleeding, particularly in premature infants or those with liver disease, may require a transfusion of fresh frozen plasma or whole blood. The mortality rate is low in treated patients.

Concentrated form of vitamin K-dependent coagulation factor should be avoided because of risk of transmitting serum hepatitis.

A particularly severe form of deficiency of Vitamin K-dependent coagulation factors has been reported in infants born to mothers receiving anticonvulsive medications (phenobarbital and phenytoin) during pregnancy. The infants may have severe bleeding, with onset within the first 24 hours of life; the bleeding is usually corrected by vitamin although in some the response is poor or delayed. A PT should be measured in cord blood, and the infant given 1–2 mg of vitamin K intravenously. If the PT is greatly prolonged and fails to improve, 10 mL/kg of fresh frozen plasma should be administered.

The routine use of intramuscular vitamin K for prophylaxis is safe and is not associated with an increased risk of childhood cancer or leukemia. Although oral vitamin K (birth, discharge, 3–4 weeks: 1–2 mg) has been suggested as an alternative, oral vitamin K is less effective in preventing the late onset of bleeding due to vitamin K deficiency and thus cannot be

recommended for routine therapy. The intramuscular route remains the method of choice.

Other forms of bleeding may be clinically indistinguishable from hemorrhagic disease of the newborn responsive to vitamin K, but they are neither prevented nor successfully treated with vitamin K. A clinical pattern identical to that of hemorrhagic disease of the newborn may also result from any of the congenital defects in blood coagulation. Hematomas, melena, and post-circumcision and umbilical cord bleeding may be present; only 5–35% of rises of factor VIII and IX deficiency become clinically apparent in the newborn period. Treatment of the rare congenital deficiencies of coagulation factors requires fresh frozen plasma or specific factor replacement.

Once correction of vitamin K deficiency is achieved, its cause must be identified so that preventive actions can be instituted to prevent a recurrence. In early-onset VKDB, this may include cessation of breastfeeding if a mother is required to take medication that interferes with vitamin K metabolism, which may be passed to the infant via breast milk. In classical VKDB, additional vitamin K administration may be required if poor feeding is an ongoing problem or if a mother insists on exclusively breastfeeding. In late-onset VKDB, correction of the underlying disorder should be undertaken, if possible, and continued vitamin K therapy (often parentally) may be required.

## PREVENTION

There is no question that vitamin K prophylaxis is effective at reducing the risk for VKDB in infants, but controversies exist regarding the route of administration and, to some extent, the dosing. The advantage of intramuscular prophylaxis, which is widely used, is its long duration of action, presumably from a depot effect. Newborns receiving intramuscular prophylaxis have increased levels of vitamin K for at least 4 weeks compared within far receiving no prophylaxis. The disadvantages are discomfort, poor acceptance by some parents, and rarely, intramuscular hematomas, local abscesses, and the potential of local nerve and vessel damage. Finally, extremely high levels of vitamin K are achieved following intramuscular injection, and it remains unknown whether this could be harmful.

Oral vitamin K prophylaxis is the preferred method. Dosing regimens vary based on local practice and guidelines. In addition to avoidance of extraordinarily high levels of vitamin K, the oral route is also more acceptable to parents.

Its principal disadvantage is that administration must continue after discharge from the hospital, leading to an increased pool of at-risk infants due to poor compliance. Regardless of the chosen method, it is vital that prophylaxis be given to all infants. In particular, babies born at home or in other nonhospital settings are at higher risk for not receiving prophylaxis, so parents should be questioned about this at first contact with the pediatrician.

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# Henoch–Schönlein Purpura

## PRESENTING COMPLAINTS

A 2-year-old boy was brought with the complaints of:

- Rashes since 1 day
- Uneasiness since 1 day

## History of Presenting Complaints

A 2-year-old boy was brought to the casualty with history of florid rash over the forearm, hands, trunk, buttocks, and lower limbs. All these developed spontaneously within last 24 hours. Mother described rashes as circular, red in color with increased redness in center. There was flushed area surrounding the rash. In spite of these rashes he was playful. In between he used to have brief episodes of uneasiness. There was no history of itching.

## Past History of the Patient

He was the only sibling of nonconsanguineous marriage. He was born at full term by normal delivery. Baby cried immediately after the delivery. The birth weight of the baby was 3 kg.

Child was given breastfeeds immediately. He was on exclusive breast milk for 4 months. Later, weaning was started at 4 months and he was on family food by 18 months. There was no postnatal significant event except for the normal physiological jaundice. Developmental milestones were normal. Child had been completely immunized.

## EXAMINATION

The boy was moderately built and nourished. He was playful and was playing with the toys on the examination table. Anthropometric measurements included height 88 cm (90th centile) and weight 13 kg (70th centile).

Child was afebrile. The pulse rate was 120 per minute and respiratory rate was 32 per minute. The blood pressure recorded was 60/40 mm Hg. The rashes were present over the forearms, hands, trunk, buttocks, and lower limbs. These rashes used to blanch on pressure.

There was no pallor, no lymphadenopathy, and no cyanosis. All the systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 10 g/dL
TLC	: 11,000 cells/cu mm
Platelets	: 450,000 cells/cu mm
PT	: 18 seconds
IgA level	: 5 g/dL (increased)
C3 complement	: Normal
Urine	: RBC++; Protein++
Stools	: Red cells+

## DISCUSSION

This is also known as anaphylactoid purpura. It is the vasculitis of small vessels. This illness is more frequent in children than adults. Most cases occur between 2 and 8 years of age. It is more common in male and in winter season.

The specific pathogenesis of Henoch–Schönlein purpura (HSP) is not known. The cytokin tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and

### CASE AT A GLANCE

#### Basic Findings

Height	: 88 cm (90th centile)
Weight	: 13 kg (70th centile)
Temperature	: 37°C
Pulse rate	: 120 per minute
Respiratory rate	: 32 per minute
Blood pressure	: 60/40 mm Hg

#### Positive Findings

##### History

- Rashes
- Sudden onset
- No itching

##### Examination

- Rashes over the lower limb and buttocks

##### Investigation

- Urine: RBC++; Protein+
- IgA level: Increased
- Stool: RBC present

interleukin-6 (IL-6) have been implicated in active disease. It is an immunoglobulin A (IgA)-mediated vasculitis. Perivascular accumulations of white cells are present.

Henoch–Schönlein purpura, recently renamed IgA vasculitis, is an acute leukocytoclastic vasculitis, affecting mainly the small vessels of the skin, joints, gastrointestinal tract, and kidneys. HSP is the most common form of systemic vasculitis in childhood.

The main features of the disease include non-thrombocytopenic palpable purpura (present in 100% of affected children), arthritis or arthralgias (75–85%), colicky abdominal pain with or without gastrointestinal (GI) hemorrhage (60–85%), and renal involvement (10–50%). Although it can occur at any age, HSP is overwhelmingly a disease of childhood. The mean age of patients is 6 years. The clinical features of HSP may be atypical at the extremes of age, typically presenting with milder manifestations in infants younger than 2 years of age and a more severe course in adults.

The disease occurs more frequently in males, although sex differences are not seen in patients older than age 16 years. HSP has a seasonal pattern, with peaks in winter and spring. It is an IgA-mediated, leukocytoclastic vasculitis characterized by neutrophil infiltration and fibrinoid necrosis in the walls of arterioles, capillaries, and postcapillary venules, with deposition of IgG, IgA, and C3.

The etiology of the disease is unknown. HSP often follows a respiratory infection. A wide variety of pathogens and other environmental exposures that have been associated with HSP include bacterial infections (group A beta-hemolytic streptococci, *Legionella*, *Yersinia*, *Mycoplasma*), viral infections (Epstein-Barr virus, varicella-zoster virus, cytomegalovirus, parvovirus, hepatitis-B virus), drugs (penicillin and other  $\beta$ -lactam antibiotics, chlorpromazine, quinidine, thiazide diuretics), vaccines (measles, yellow fever, cholera), food additives, and insect bites. Of all the pathogens linked to HSP, group A beta-hemolytic *Streptococcus* has been studied the most.

#### GENERAL FEATURES

- Acute onset
- Fatigue
- Rash—maculopapular, petechiae, purpura
- Renal involvement

#### CLINICAL FEATURES (FIG. 1)

Onset of the disease may be acute or insidious. There will be low-grade fever and fatigue.

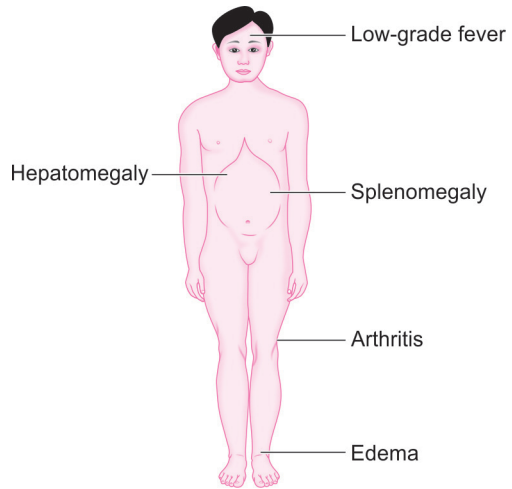


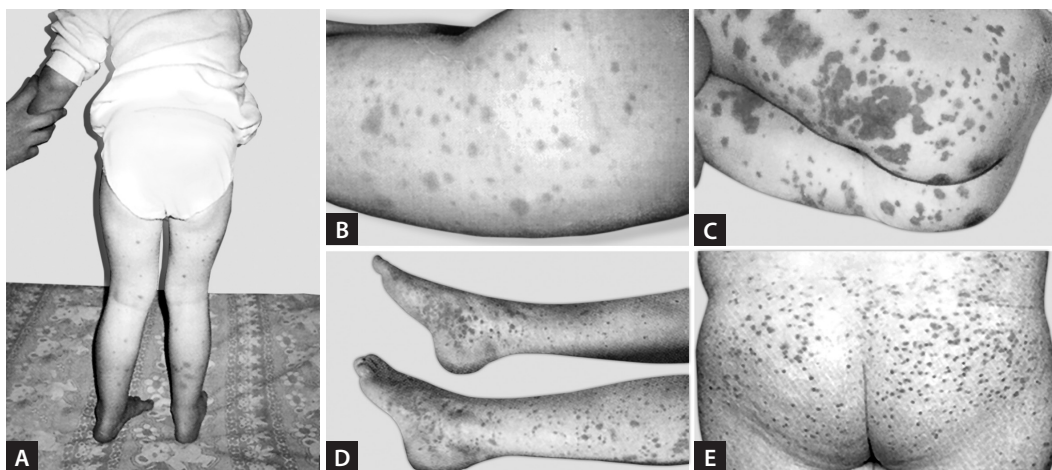
Fig. 1: Clinical features.

Headache, loss of appetite and abdominal pain are early symptoms. It is a benign self-limiting disease which resolves after fluctuating course. It involves GI tract, renal system and joints.

The hallmark of the disease is rash. Initially, they begin as pinkish maculopapules which blanch on pressure. These may progress to petechiae or purpura. These are palpable purpura that evolve from red to purple to rusty brown. These tend to occur in crops. These last from 3 to 10 days. These appear on legs and feet above the knees and buttocks. This condition can easily be distinguished from other causes because platelet count is in normal range. Damage to the cutaneous vessels results in local angioedema. Edema occurs primarily in dependent areas such as waist, eyes and buttocks.

Skin lesions, present in all patients because the diagnosis depends on a recognizable rash, are the initial manifestation in about 50% of patients. The typical rash begins as small wheals or erythematous maculopapules that evolve into petechial or purpuric lesions, more prominent on dependent and pressure-bearing area. Although usually located over the lower extremities or buttocks, the rash may involve the upper extremities, trunk, and face. In young children, HSP might present as edema and purpura involving the face and ears. Skin lesions tend to occur in crops and last from 5 days to 4 weeks. Angioedema of the scalp perineal area, and extremities may precede the onset of the rash (Figs. 2A to E).

Arthritis is localized to knee and ankles. These manifest as periarticular pain, tenderness and



**Figs. 2A to E:** Henoch–Schönlein purpura.  
(For color version see Plate 1)

minimal swelling. These will be associated with concomitant of edema. The effusions are serous and not hemorrhagic. There will resolve without any residual deformity and articular damage.

Arthritis is the second most common feature of HSP, occurring in roughly 75% of patients and most often affecting knees and ankles. In about 25% of patients, arthritis/arthralgias of large joints are the initial symptom of HSP, often preceding the appearance of a skin rash by 24–48 hours. Because joint swelling is often periarticular, there may be no true joint effusion despite significant pain on motion. Joint symptoms typically resolve spontaneously after a few days without residual deformity but may recur with exacerbations or recurrences of HSP.

Gastrointestinal involvement occurs in 50–75% of patients. The most common complaint is colicky abdominal pain, frequently associated with vomiting. Pain may be severe enough to mimic an acute abdomen and may precede the onset of rash in as many as 10–15% of patients, again confusing the clinical picture. GI bleeding is usually occult, but 30% of patients have grossly bloody or melanic stools. Upper GI series show nonspecific changes such as thickening of the bowel wall, *thumb printing*, and filling defects. Ultrasound studies are abnormal in as many as 80% of patients with GI involvement and reveal increased echogenicity and thickening of the wall of the second portion of the duodenum and/or hydrops of the gallbladder. Endoscopy may reveal lesions with similar appearance to the palpate purpura seen in the skin. These findings are not present

in patients with HSP without GI complaints. Intussusception has been reported in 1–5% of patients; other uncommon complications may include perforation or bowel infarct.

Edema and damage to gastrointestinal tract may lead to intermittent abdominal pain. This is often colicky in nature. Some may have hematemesis, melena and diarrhea. There will be associated, intussusception, perforation, and bowel obstruction.

Renal involvement occurs in 40–50% of patients with HSP and is most commonly limited to transient urinary abnormalities such as microscopic hematuria or hematuria plus mild proteinuria. Unlike arthritis and GI involvement, nephritis rarely, if ever, precedes the onset of purpura. Patients with nephritis develop urinary abnormalities within 4 weeks, but they may occur up to 3 months after the onset of symptoms. Urinalysis should be done each week while the disease is active, then monthly for the next 3 months: If all analyses are normal, nephritis is unlikely to occur. If at any time there is evidence of nephritis, long-term monitoring of urinalyses, protein excretion, renal function, and blood pressure is warranted until the urinary abnormalities resolve. Renal histopathology shows lesions indistinguishable from those of IgA nephropathy (Berger's disease).

Renal involvement occurs in about 25–50% of the children. These are limited to hematuria, leading to chronic renal failure, nephritis and nephrotic syndrome. There will be focal segmental increase in mesangial cells and matrix.

**CLINICAL FEATURES**

- Acute onset
- Low-grade fever
- Fatigue
- Rash—maculopapular, petechiae, purpura
- Arthritis
- Edema
- Hepatosplenomegaly
- Renal involvement

Central nervous system involvement leads to development of seizures, paresis and coma. Other rare complications include rheumatoid like nodules, cardiac and eye involvement mononeuropathies, pancreatitis, pulmonary, and intramuscular damage.

**DIAGNOSIS****Diagnostic Criteria**

Purpura or petechiae are (mandatory) more extensive in the lower extremities and one of the following four criteria:

1. Abdominal pain
2. Histopathology (IgA deposition on biopsy)
3. Arthritis or arthralgia
4. Renal involvement

Routine laboratory tests are neither specific nor diagnostic. There will be moderate thrombocytosis and leukocytosis. ESR may be raised. Anemia may be present. Immunofluorescent microscopy reveals mesangial deposits of IgA, frequently in association with IgG, C3 and fibrin. The predominant deposits of IgA suggest IgA nephropathy. Definitive diagnosis is confirmed by biopsy of the involved cutaneous sites. Elevated levels of ASLO titer are noted.

**DIFFERENTIAL DIAGNOSIS**

- Meningococcemia
- Systemic lupus erythematosus (SLE)
- Polyarteritis nodosa
- Goodpasture syndrome
- Kawasaki disease

**COMPLICATIONS**

- Nephrotic syndrome
- Bowel perforation
- Scrotal swelling
- Chronic renal disease

**TREATMENT**

Treatment is largely supportive. Most children may be managed as outpatients with appropriate analgesia and hydration. Development of GI and renal complications may be monitored by assessing stool guaiac tests, blood pressure, and urine dipsticks as an outpatient, unless severe intestinal or renal involvement necessitates hospital admission.

Antibiotics are given for streptococcal infection. Steroids are helpful in arthralgia and abdominal pain. Hydration of the patient should be corrected by intravenous fluid and/or by plenty of oral fluid. Diet should be easily digestible to the gut of the patient. Acetaminophen is used to control pain, edema, fever, and malaise. Other associated systemic diseases are managed accordingly.

Intestinal complication (e.g., hemorrhage, obstruction and intussusception) may be life-threatening and managed with corticosteroids, barium enema reduction, surgical reduction or resection of intussusception. Oral or intravenous corticosteroids (1–2 mg/kg/day) are often associated with the dramatic improvement of both GI and CNS complication.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used to manage severe joint pain, although they should be avoided in the setting of significant renal disease. Prednisone in a dosage of 1–2 mg/kg/day is helpful in the management of painful edema, scrotal swelling, and severe, disabling arthritis. Steroids also may be used in children with severe abdominal pain, although its efficacy has not been proven. Treatment of HSP nephritis remains controversial. Therapies of severe renal disease, particularly chronic changes such as crescent formation, include intravenous pulses of methylprednisolone, cyclophosphamide, and azathioprine, alone or in different combinations.

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# Hereditary Spherocytosis

## PRESENTING COMPLAINTS

A 10-year-old boy was brought with the complaints of:

- Cough and cold since 1 week
- Throat pain since 3 days
- Decreased appetite since 3 days
- Abdominal pain since 1 day

## History of Presenting Complaints

A 10-year-old boy was presented to the casualty with history of abdominal pain. Pain was present on left upper part of the abdomen. It was severe colicky pain. It was present since day 1. It was not related to bowel and bladder disturbances. It was not related to food intake. One week back child had received treatment for cough, cold and throat pain. There was no history of vomiting and disturbed sleep. According to the mother the child's appetite has come down.

## Past History of the Patient

This boy was the eldest sibling of nonconsanguineous marriage. He was born at full term by

normal delivery. There was no significant post-natal event. His developmental milestones were normal. His performance at school was normal.

## EXAMINATION

On examination, the patient was moderately built and nourished. He was looking sick because of the abdominal pain. The anthropometric measurements included, the height was 132 cm (50th centile) and the weight was 28 kg (50th centile).

He was febrile. The pulse rate was 106 per minute and the respiratory rate was 26 per minute. The blood pressure recorded was 110/80 mm Hg. Pallor and icterus were present. There was no lymphadenopathy and no clubbing.

Throat examination revealed presence of enlarged congested tonsils. Per abdomen examination revealed splenomegaly about 4 cm below left costal margin. It was tender and soft on palpation. Cardiovascular system examination revealed presence of ejection systolic murmur at the base. There was no radiation of the murmur. Other systemic examinations were normal.

## CASE AT A GLANCE

### Basic Findings

Height	: 132 cm (50th centile)
Weight	: 28 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 106 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 100/80 mm Hg

### Positive Findings

#### History

- Upper respiratory tract infection (URTI)
- Abdominal pain

#### Examination

- Pallor
- Icterus
- Splenomegaly

#### Investigation

- *Bilirubin*: Raised
- *Peripheral blood smear*: Small round red cells
- *Coombs' test*: Negative

## INVESTIGATION

Hemoglobin	: 9 g/dL
TLC	: 38,600 cells/cu mm
Serum bilirubin	: 4.9 g/dL unconjugated bilirubin is raised
Mean corpuscular volume (MCV)	: 60 fL
MCHC	: More than 36%
Platelet count	: 250,000 cells/cu mm
Reticulocyte count	: 2%
Osmotic fragility test	: Increased
Peripheral blood smear	: Small red round cells
X-ray skull	: Showed widening of diploic space in the frontal and parietal bones
Coombs' test	: Negative
Urine	: Normal



## DISCUSSION

The child is anemic and icteric. Raised serum bilirubin is unconjugated type and is the indicator of hemolysis. Pancytopenia is present. Reticulocyte count was low as a result of hemolysis. Negative Coombs' test indicates bone marrow hypoplasia.

Hereditary spherocytosis (HS) usually is transmitted as an autosomal dominant or, less commonly, as an autosomal recessive disorder. About 25% of patients have no previous family history. The pathophysiology underlying HS involves five proteins, which are key components of the cytoskeleton responsible for red blood cell (RBC) shape.

## PATHOGENESIS

Abnormalities of spectrin or ankyrin are the most common molecular defects. Dominant defects have been described in  $\beta$ -spectrin and band 3. Recessive defects have been described in  $\alpha$ -spectrin and protein 4.2. Both dominant and recessive defects have been described in ankyrin.

A deficiency in spectrin, band 3, ankyrin, or protein 4.2 results in uncoupling in the "vertical" interactions of the lipid bilayer skeleton and subsequent release of membrane microvesicles. The most common molecular defects are abnormalities of the spectrin or ankyrin. The loss of membrane surface area without a proportional loss of cell volume causes spherizing of the RBCs. There is associated increase in cation permeability, cation transport, adenosine triphosphate use, and glycolysis. The decreased deformability of the spherocytic RBCs impairs cell passage from the splenic cords to the splenic sinuses, and the spherocytes are destroyed prematurely in the spleen. The decreased abnormality of the spherocytic RBCs impairs cell passage from the splenic cords to splenic sinuses. The spherocytic RBCs are destroyed prematurely in the spleen. Splenectomy improves the RBCs lifespan and cures anemia.

Defects in the erythrocyte membrane lead to loss of membrane surface area and eventual morphologic change. Spherocytes have a decreased ability to deform and quickly become trapped in the sinusoids of the spleen; the majority of hemolysis in spherocytosis thus occurs in the extravascular compartment.

Characteristic spherocytic red cell is smaller than normal erythrocyte and lacks the central pallor of the biconcave disc when the red cells are placed in hypotonic saline solution. Water and sodium enter the cell and causing them to swell.

Hereditary spherocytosis and  $\beta$ -thalassemia should be considered as spleen was palpable and red cells were microcytic. Coombs' test will be positive if there is autoimmune process. Acute leukemia with pancytopenia is ruled out because of the presence of unconjugated bilirubin.

Children with congenital hemolytic disease may develop acute hemolytic crisis or an aplastic crisis. Acute hemolytic crisis is caused by hemolytic episodes provoked by antimalarials. Reticulocyte count remains increased in glucose-6-phosphate dehydrogenase (G6PD). But the test should be repeated once acute episode was resolved, and reticulocyte count would have returned normal.

*Other possible diagnoses include:*

- Paroxysmal cold hemoglobinuria is usually precipitated by viral infection.
- Autoimmune hemolytic anemia in which Coombs' test is negative.
- *Cold agglutination disease:* This follows viral infection especially by *Mycoplasma*.
- *Congenital hemolytic anemia:* X-linked inheritance should be explained to the parents. They should be alarmed of the provoking factors such as infections and drugs.

Hereditary spherocytosis is associated with splenomegaly with the red cells that are spherical in shape. Affected cells are unduly permeable to sodium and acquire the spherocytic shape because of loss of membrane function and increase in volume.

Spleen is intimately involved in hemolytic process. Splenic circulation imposes metabolic environment that is characterized by stressful spherocytic cells. Repeated passage through the splenic circulation produces sequestration and destruction. The spherocyte is relatively rigid and passes with difficulty through the minute apertures between splenic cord and sinuses.

In neonates, it may manifest with anemia and hyperbilirubinemia, slight jaundice may be present after infancy. This may be enough to require phototherapy and exchange transfusion. Spleen is almost always palpable. Pigmentary gallstones have been reported as early as 4–5 years of age.

Evidence of hemolysis includes reticulocytosis, anemia and hyperbilirubinemia. Abnormality of the red cell membrane can be demonstrated by osmotic fragility studies.

Because of the high RBCs turnover and high tuned erythroid marrow activity, children are prone to aplastic crisis. This occurs as a result of parvovirus.

The diagnosis can be made on the triad of spherocytosis, increased osmotic fragility and dominant inheritance.

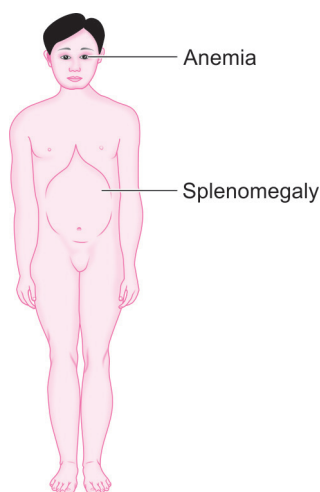
## CLINICAL FEATURES (FIG. 1)

In the neonatal period, HS is a significant cause of hemolytic disease and can be manifest as anemia and hyperbilirubinemia sufficiently severe to require phototherapy or exchange transfusions. Hemolysis may be more prominent in the newborn because hemoglobin F binds 2,3-diphosphoglycerate (2,3-DPG) poorly, and the increased level of free 2,3-DPG destabilizes interactions among spectrin, actin, and protein 4.1 in the RBC membrane.

Some patients remain asymptomatic into adulthood, but others have severe anemia with pallor, jaundice, fatigue, and exercise intolerance. Severe cases may be marked by expansion of the diploë of the skull as a result of marrow hyperplasia (frontal bossing), but to a lesser extent than in thalassemia major. Depending on the severity of the anemia and the comorbidities associated with severe anemia, some patients benefit from a splenectomy.

After infancy, splenomegaly is common; there is no correlation between spleen size and disease severity. Bilirubin gallstone formation is a function of age; they can form as early as age 4–5 years and are present in the majority of adult patients.

Children with HS are also susceptible to aplastic crises, primarily as a result of parvovirus B19 infection, and to hypoplastic crises associated with various other infections turnover in the setting of erythroid marrow failure can result in profound anemia (hematocrit <10%), high-output heart failure, cardiovascular collapse, and death. White blood cell and platelet counts can also fall.



**Fig. 1:** Clinical features.

Rare complications associated with HS include splenic sequestration crisis, gout, cardiomyopathy, priapism, leg ulcers, and spinocerebellar degeneration.

Typical manifestations of spherocytosis include partially compensated hemolysis with variable anemia and substantial reticulocytosis. Affected children have intermittent jaundice and palpable splenomegaly, and are at risk for developing pigmented (bilirubin) gallstones due to chronic hemolysis. Because of the dependence on an active marrow output of reticulocytes, severe anemia requiring erythrocyte transfusion (aplastic crisis) can occur in association with acute parvovirus B19 infection, and may be the initial clinical presentation. In the newborn period, spherocytosis is often associated with nonphysiologic jaundice in the first 24 hours of life; anemia may be exaggerated during the 1st year of life requiring periodic RBC transfusions.

Spherocytosis should be considered in any child with anemia, especially if there is a positive family history and splenomegaly. The complete blood count shows mild-to-moderate anemia with an increased reticulocyte but normal leukocyte and platelet counts. The mean corpuscular hemoglobin concentration (MCHC) is often increased and virtually pathognomonic for spherocytosis when greater than 36 g/dL. Small, dense spherocytes without central pallor can be identified on the peripheral smear, along with larger reticulocytes. A negative direct antiglobulin test (DAT; formerly known as the direct Coombs' test) excludes an autoimmune hemolytic process. The gold standard to establish the diagnosis of spherocytosis is to demonstrate an increased osmotic fragility; this testing may not be required if clinical presentation and family history are consistent with spherocytosis.

### FEATURES OF HEMOLYTIC ANEMIA

- Dark colored urine; dark brown or red
- Jaundice
- Pallor
- Tachycardia
- Spleen and liver enlargement

## LABORATORY FINDINGS

The diagnosis of HS can be established from a positive family history and the presence of typical clinical and laboratory features of the disease: splenomegaly, spherocytes on the blood smear, reticulocytosis, and an elevated mean corpuscular hemoglobin concentration. If these are present,

no additional testing is necessary to confirm the diagnosis.

The classic incubated osmotic fragility test can detect the presence of spherocytes in the blood; however, it is not specific to HS and may be abnormal in other hemolytic anemias. The RBCs are incubated in progressive dilutions of sodium chloride causing the RBCs to swell and eventually lyse. Spherocytes lose at a higher sodium chloride concentration than biconcave cells in hypotonic solutions because they have a lower surface area to volume ratio. Unfortunately, this test has poor sensitivity relative to other screening assays and can miss up to 20% of mild HS cases.

Evidence of hemolysis includes and indirect hyperbilirubinemia. The hemoglobin level usually is 6–10 g/dL, but it can be in the normal range. The reticulocyte percentage is often increased to 6–20%, with a mean of approximately 10%. The mean corpuscular volume is normal, although the mean corpuscular hemoglobin concentration often is increased (36–38 g/dL, RBCs). The RBCs on the blood smear vary in size and include polychromatophilic reticulocytes and spherocytes. MCHC is increased. X-ray shows erythroid hyperplasia. The spherocytes are smaller in diameter and appear hyperchromic as a result of the high hemoglobin concentration. The central pallor is less conspicuous than in normal cells. Spherocytes may be the predominant cells or may be relatively sparse, depending on the severity of the disease. Other evidence of hemolysis includes decreased haptoglobin and the presence of gallstones on ultrasonography.

The presence of spherocytes can be confirmed by osmotic fragility test. The rare causes of spherocytes include thermal injury, clostridia septicemia and Wilson's disease.

Clinically, HS should be differentiated from other inherited disorders presenting with episodic anemia, jaundice and splenomegaly, such as other red cell membranopathies, enzymopathies, unstable Hb and autoimmune hemolytic anemia.

#### LABORATORY SALIENT FINDINGS

- Spherocytosis
- Reticulocytosis
- Negative Coombs' test
- Elevated indirect bilirubin
- Increased osmotic fragility
- Erythroid hyperplasia
- Splenomegaly, gallstones
- Elevated mean corpuscular hemoglobin concentration (MCHC)

#### GENERAL FEATURES

- Hyperbilirubinemia
- Fatigue
- Exercise intolerance
- Pigmentary gallstones

#### DIFFERENTIAL DIAGNOSIS

- ABO incompatibility
- Isoimmune hemolytic anemia
- Thermal injury
- Clostridia septicemia
- Wilson's disease

#### ESSENTIAL DIAGNOSTIC POINTS

- Anemia and jaundice
- Family history of jaundice gallstones
- Splenomegaly
- Spherocytosis with reticulosis
- Increased osmotic fragility
- Negative Coombs' test

#### TREATMENT

##### General Supportive Care

Parents should be advised of the risk of newborn jaundice and the potential need for phototherapy and exchange transfusion after birth to decrease bilirubin levels. Infants born to parents with known HS should be monitored carefully as hyperbilirubinemia may peak several days after birth. A minority of infants will be transfusion-dependent until development of adequate erythropoiesis to compensate for the ongoing hemolysis. Continued transfusion-dependence is not common after 6–12 months of age.

Once the baseline level of disease severity is reached, an annual visit to the hematologist usually is sufficient. Growth should be monitored, exercise tolerance and spleen size should be documented, and parents should receive anticipatory guidance regarding the risk of aplastic crisis secondary to parvovirus, and hypoplastic crises with other infections. Parents and patients should be informed of an increased risk for gallstone development. The degree of splenomegaly does not correlate with disease severity. Folic acid supplementation is recommended in moderate and severe HS because of an enhanced requirement with increased erythropoiesis.

Treatment is splenectomy. It should be delayed until the patient is 5–6 years old. If anemia is severe enough to impair growth or if aplastic crisis is frequent, the operation may be considered earlier.

Red blood cell transfusion can be given during an aplastic crisis. Splenectomy prevents gallstones

and eliminates the threat of aplastic crisis. After splenectomy, jaundice and reticulocytosis disappear. Immunization against *Haemophilus influenzae* type b, *Streptococcus pneumoniae* and *Neisseria meningitidis* should be done. Post-splenectomy, patients should receive penicillin, to prevent sepsis. Patient should receive folic acid supplementation to prevent deficiency due high turnover of red cells and accelerated erythropoiesis throughout life.

## INDICATIONS FOR SPLENECTOMY

- Severe anemia
- Reticulocytosis
- Aplastic crisis
- Poor growth
- Cardiomegaly

## GUIDELINES FOR SPLENECTOMY

Because the spherocytes are destroyed almost exclusively in the spleen, splenectomy eliminates most of the hemolysis. After splenectomy, the anemia, hyperbilirubinemia, and incidence of gallstones are significantly lessened, if not completely eradicated. However, splenectomy is associated with immediate surgical morbidities in addition to a lifelong increased risk for sepsis, particularly that caused by pneumococcal species. This risk is not completely eliminated with the requisite pre- and postoperative vaccination against *Pneumococcus*, *Meningococcus*, and *Haemophilus influenzae* type b.

Splenectomy is recommended for patients with severe HS. It should be considered for patients with moderate HS and frequent hypoplastic or aplastic crises, poor growth, or cardiomegaly. It is generally not recommended for patients with mild HS. When splenectomy is indicated, it should be performed after the age of 6 years, if possible, to avoid the heightened risk of post-splenectomy sepsis in younger children.

The laparoscopic approach has less surgical morbidity and is recommended if the surgeon is adequately trained in this approach. Partial splenectomy may be beneficial but needs further study. In children undergoing splenectomy, a concomitant cholecystectomy should be performed if there are gallstones. It is controversial whether to perform a concomitant splenectomy in less-severely ill patients who are undergoing cholecystectomy for gallstone disease. Postsplenectomy thrombocytosis is commonly observed, but requires no treatment and usually resolves spontaneously.

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# Idiopathic Thrombocytopenic Purpura

## PRESENTING COMPLAINTS

A 3-year-old girl was brought with the complaints of:

- Cough and cold since 2 weeks
- Fever since 3 days
- Rashes since 1 day
- Bleeding in mucous membrane of mouth

## History of Presenting Complaints

A 3-year-old girl presented with the history of sudden onset of bruising and generalized rashes all over the body. There was history of bleeding in mucous membrane of mouth in gum and lips. There was bleeding in nose also. There was no itching. There was past history of cough and cold, which had been treated by family doctor about 2 weeks before.

## Past History of the Patient

She was the eldest sibling of nonconsanguineous marriage. She was born at full term after normal

delivery. She cried immediately after the delivery. There was no significant postnatal event. Child's developmental milestones were normal. Her performance at school was good.

## EXAMINATION

The girl was moderately built and moderately nourished. She was sitting quiet on the examination table. Anthropometric measurements included height was 95 cm (50th centile) and weight was 13 kg (50th centile).

The child was afebrile. The pulse rate was 120 per minute and the respiratory rate was 20 per minute. The blood pressure recorded was 60/44 mm Hg. There was no pallor, no lymphadenopathy, no icterus, and no edema.

There was hematoma on the upper lip. Bleeding from the gingiva was present. There were multiple bruises of varying size and color. Superficial macular non-blanching erythematous rashes were present over the eyelids and cheeks. There was a fresh gaze over the skin with marked bruising and hematoma over the left side of the forehead as well as over the right flank and left knee.

## CASE AT A GLANCE

### Basic Findings

Height	: 95 cm (50th centile)
Weight	: 13 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 120 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 60/44 mm Hg

### Positive Findings

#### History

- Rashes
- Cough and cold 15 days back
- Bleeding in gum

#### Examination

- Hematoma
- Bleeding in gingival region
- Macular non-blanching erythematous rashes

#### Investigation

- BT prolonged
- Platelet decreased
- Peripheral blood smear shows large platelets
- Bone marrow examination reveals increased megakaryocytes

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 7,800 cells/cu mm
Platelet count	: 40,000/cu mm
Bleeding time (BT)	: 6 minutes (1-5 minutes)
Clotting time (CT)	: 7 minutes (4-8 minutes)

Erythrocyte sedimentation rate (ESR)	: 12 mm in the 1st hour
Peripheral blood smear	: Megathrombocytes, i.e., large platelets are seen

Bone marrow examination	: Normal granulocytes and erythrocytic series, increased number of eosinophils and megakaryocytes.
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## DISCUSSION

The child had a preceding viral infection. This is followed by acute onset of bruises and petechiae. Generalized petechiae are suggestive of thrombocytopenia. Leukemia is ruled out as there is absence of pallor and lymphadenopathy, and the features are suggestive of bone marrow failure. It is the most common acquired bleeding disorder. It is a benign disorder.

About 70% of the idiopathic thrombocytopenic purpura (ITP) follows lower respiratory tract infection (LRTI). This may act as trigger factor, where an immune process results in development of platelet antibodies. Bone marrow aspirate shows normal or increased number of megakaryocytes. Every common infectious virus has been described in association with ITP including Epstein–Barr virus (EBV) and HIV.

In a small number of children, 1–4 weeks after exposure to a common viral infection, an autoantibody directed against the platelet surface develops with resultant sudden onset of thrombocytopenia. A recent history of viral illness is described in 50–65% of cases of childhood ITP. The peak age is 1–4 years, although the age ranges from early in infancy to the elderly. In childhood, males and females are equally affected. ITP seems to occur more often in late winter and spring after the peak season of viral respiratory illness. The most common cause of acute onset of thrombocytopenia in an otherwise well child is (autoimmune) ITP.

## PATHOGENESIS

Immune thrombocytopenia is an acquired disorder that has a multifactorial etiology including generation of antiplatelet auto-antibodies and subsequent reticuloendothelial clearance, direct T-cell cytotoxicity, and abnormal platelet production in the bone marrow.

Some children develop the acute presentation of an autoimmune disease is unknown. The exact antigenic target for most such antibodies in most cases of childhood acute ITP remains undetermined. Although in chronic ITP, many patients demonstrate antibodies against the platelet glycoprotein complex. After binding of the antibody to the platelet surface, circulating antibody-coated platelets are recognized by the Fc receptor on splenic macrophages, ingested, and destroyed. Most common viruses have been described in association with ITP, including EBV and HIV. EBV-related ITP is usually of short duration and follows the course of infectious mononucleosis.

HIV-associated ITP is usually chronic. In some patients, ITP appears to arise in children infected with *Helicobacter pylori* or rarely following vaccines.

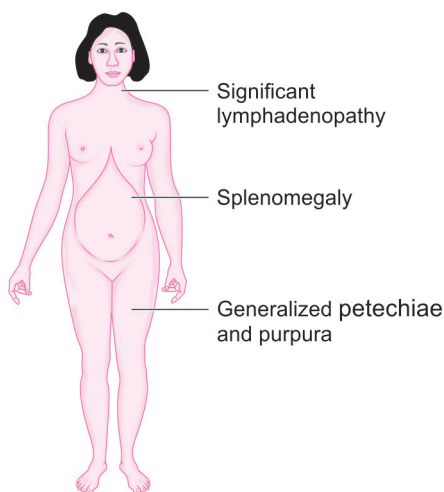
Platelet-associated immunoglobulin can be demonstrated in plasma of patients. It is attributed to the interaction of the platelets and immune complex formed during antibody response to viral infection. The platelets are sequestered in the spleen and survival time is diminished.

It is associated with petechial and mucocutaneous bleeding and occasionally, it hemorrhages into the tissue. There is profound deficiency of circulating platelet despite adequate number of megakaryocytes in bone marrow. Increased amount of immunoglobulin G (IgG) has been found bound to platelets and may represent immune complexes absorbed on the platelet surface.

## CLINICAL FEATURES (FIG. 1)

The classical presentation is sudden onset of generalized petechiae (**Fig. 2**) and purpura (**Fig. 3**). This occurs in healthy child between 1 and 4 years age. There will be history of preceding viral infection 1–4 weeks with average of 2 weeks. Hemorrhage in mucous membrane may be prominent with hemorrhagic bullae on the gums and lips. Nasal bleeds may be severe. Findings on physical examination are normal, other than the finding of petechiae and purpura. Splenomegaly, lymphadenopathy, bone pain, and pallor are rare.

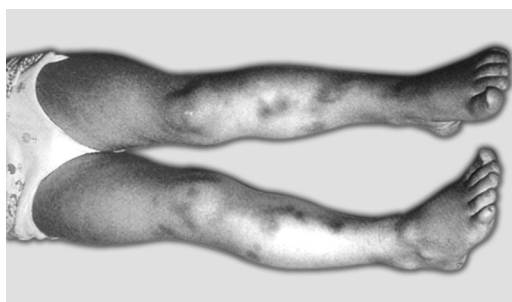
Immune thrombocytopenia diagnosis is classified as either primary or secondary. Primary ITP, or ITP not triggered by another disorder, occurs in up to 75% of children. Secondary ITP is that triggered by



**Fig. 1:** Clinical features.



**Fig. 2:** Petechial rashes.  
(For color version see Plate 2)



**Fig. 3:** Purpura.  
(For color version see Plate 2)

another disorder, including autoimmune diseases, immunodeficiency syndromes, thyroid disease, infection, or pregnancy.

*ITP can be clinically classified on the basis of symptoms and signs as:*

- No symptoms
- *Mild symptoms:* Bruising and petechiae, occasional minor epistaxis, and very little interference with daily living
- *Moderate symptoms:* More severe skin and mucosal lesions; more troublesome epistaxis and menorrhagia
- *Severe symptoms:* Bleeding episodes—menorrhagia, epistaxis, melena—requiring transfusion or hospitalization; symptoms interfering seriously with the quality of life.

The presence of abnormal findings such as hepatosplenomegaly, bone or joint pain, remarkable lymphadenopathy suggests cytopenias, or congenital anomalies suggest other diagnoses (leukemia, syndromes). The possibility of systemic

illness is considered in chronic ITP. The onset is insidious and occurs in adolescent.

The course of illness is benign and self-limiting spontaneous remissions occur within few weeks. Severe bleeding is rare in 70–80% of children who present with acute ITP, spontaneous resolution occurs within 6 months. Therapy does not appear to affect the natural history of the illness. 1% of patients develop an intracranial hemorrhage (ICH). There is no evidence that therapy prevents serious bleeding. Approximately 20% of children who present with acute ITP go on to have chronic ITP. The prognosis may be related more to age, as ITP in younger children is more likely to resolve whereas the development of chronic ITP in adolescents approaches 50%.

The serious complication is ICH. Petechiae may be seen all over the body, over the bony prominence and anterior surface of the leg. Spleen is often not palpable but tip of the spleen is just palpable. The presence of splenomegaly with thrombocytopenia requires aggressive evaluation of associated problems such as collagen vascular disorders and hypersplenism.

The chronic idiopathic thrombocytopenic purpura persists for more than 6 months. Some children are steroid responsive and dependent. Splenectomy may be eventually indicated but a late spontaneous remission may be the possibility. They also interfere with sequestration of platelets by the spleen as they prevent the interaction of sensitized lymphocytes in spleen with homologous platelets.

#### GENERAL FEATURES

- Sudden onset of generalized petechiae and purpura
- Bleeding from the gums and mucous membrane
- Intracranial hemorrhage

#### DIAGNOSIS

Diagnosis is chiefly based upon the clinical history, physical examination and evidence of thrombocytopenia in peripheral smear.

Severe thrombocytopenia (platelet count  $<20 \times 10^9/L$ ) is common, and platelet size is normal or increased, reflective of increased platelet turnover. In acute ITP, the hemoglobin value, white blood cell (WBC) count, and differential count should be normal. Hemoglobin may be decreased if there have been profuse nosebleeds or menorrhagia. Laboratory evidence reveals isolated thrombocytopenia with normal coagulation profile (PT and PTT). Platelet-associated IgG antibodies have been demonstrated in patients with idiopathic thrombocytopenic purpura.

Bone marrow examination is recommended only in circumstances where the diagnosis is not clear due to the presence of atypical features. Indications for bone marrow aspiration/biopsy include an abnormal WBC count or differential or unexplained anemia as well as findings on history and physical examination suggestive of a bone marrow failure syndrome or malignancy. Current recommendations do not include routine bone marrow studies prior to initiating steroid treatment or in the case of a patient who fails intravenous immunoglobulin (IVIG) therapy. Bone marrow examination is essential to exclude acute leukemia. Bone marrow examination shows normal granulocytic and erythrocytic series, with characteristically normal or increased numbers of megakaryocytes. Some of the megakaryocytes may appear to be immature and are reflective of increased platelet turnover.

Thrombopoietin levels are not recommended, as they are often not increased despite increased peripheral destruction. This observation led to the development of new therapies with recombinant thrombopoietin agonists.

Other laboratory tests should be performed as indicated by the history and physical examination. HIV studies should be done in at-risk populations, especially sexually active teens. Platelet antibody testing is seldom useful in acute ITP. A direct antiglobulin test (Coombs' test) should be done if there is unexplained anemia to rule out Evans syndrome (autoimmune hemolytic anemia and thrombocytopenia) or before instituting therapy with IV anti-D.

Direct antiglobulin test (DAT; formerly known as direct Coombs' test) and serum immunoglobulins are recommended in all newly diagnosed ITP patients, as these markers may be associated with an underlying tendency toward autoimmunity. Antinuclear antibody (ANA) testing can be obtained in patients with high suspicion for autoimmune disease.

#### LABORATORY SALIENT FINDINGS

- Thrombocytopenia
- IgG antibodies
- Normal coagulation profile
- Bone marrow—increased number of megakaryocytes

#### DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes congenital syndrome such as a megakaryocytic cytopenia, DIC, hemolytic uremic syndrome, HIV and lymphoma.

#### CLINICAL COURSE

In approximately 75% of children, ITP is a self-limited condition with spontaneous resolution regardless of interventions and treatments during the course of the disease. After remission, the chance of having another episode of ITP is small (<5%), and following recovery, children are not at increased risk for other blood disorders or cancers. The most feared outcome, ICH, is fortunately rare, occurring in less than 1% of affected children. The International Working Group Consensus Report recommends the following categories to stratify ITP cases according to duration of the disease in order to facilitate guidance and treatment decisions:

- *Newly diagnosed:* 0–3 months from diagnosis
- *Persistent:* 3–12 months from diagnosis
- *Chronic:* >12 months from diagnosis

This categorization was changed from the former terminology (acute <6 months and chronic >6 months, from diagnosis) due to the large number of children entering spontaneous remission beyond 12 months from diagnosis.

#### COMPLICATIONS

Severe hemorrhage and bleeding into the vital organs and ICH are more serious. The most risk factor for hemorrhage is platelet count less than 10,000/dL.

#### ESSENTIAL DIAGNOSTIC POINTS

- Decreased platelet count
- Petechiae
- Ecchymosis
- Normal coagulation profile
- Bone marrow—normal or increased megakaryocyte

#### TREATMENT

Acute ITP has a self-limiting and benign course. By 1 year, only 10% of children with ITP remain thrombocytopenic. The chronic ITP still improve as long as 5–10 years after the diagnosis. About 5% of patients have recurrent ITP. Recovery occurs in 50–60% of the children within 4–6 weeks and remaining within 6 months. The mortality rate in majority varies between 0.5 and 1%. It is mainly due to ICH and severe gastrointestinal hemorrhage.

*Indications for treatment include:*

- Platelet count below  $20 \times 10^9/L$
- Presence of severe mucosal bleeds
- Presence of menorrhagia
- Chronic ITP
- Symptomatic with atypical presentation

There are no data showing that treatment affects either short- or long-term clinical outcome of ITP. Many patients with new-onset ITP have mild symptoms, with findings limited to petechiae and purpura on the skin, despite severe thrombocytopenia. Compared with untreated control subjects, treatment appears to be capable of inducing a more rapid rise in platelet count to the theoretically safe level of  $>20 \times 10^9/L$ .

## Acute ITP

Given the typically mild clinical symptoms and expectation of resolution in childhood ITP, most experts recommend observation without treatment regardless of the platelet count in children with no symptoms or with only mild cutaneous findings. However, for children with “wet bleeding” symptoms, including wet purpura, epistaxis, or menorrhagia, treatment is recommended to elevate the platelet count to a hemostatic range, facilitating cessation of bleeding and decreasing the risk of ICH and other forms of life-threatening bleeding. Treatment to raise the platelet count and lessen bleeding symptoms includes corticosteroids, IVIG, and anti-D immunoglobulin. These frontline therapies function at least in part by interfering with immune destruction of antibody-coated platelets. Initial approach to the management of ITP include the following:

- *No therapy* other than education and counseling of the family and patient for patients with minimal, mild, and moderate symptoms, as defined earlier. This approach emphasizes the usually benign nature of ITP and avoids the therapeutic roller coaster that ensues once interventional therapy is begun. This approach is far less costly, and side effects are minimal.
- “A single dose of IVIG (0.8–1.0 g/kg/day) or a short course of corticosteroids should be used as first-line treatment.” IVIG at a dose of 0.8–1.0 g/kg/day for 1–2 days induces a rapid rise in platelet count (usually  $>20 \times 10^9/L$ ) in 95% of patients within 48 hours. IVIG appears to induce a response by down regulating Fe-mediated phagocytosis of antibody-coated platelets. Side effects include fever and chills during the infusion, headache, and rarely, aseptic meningitis. IVIG therapy is both expensive and time-consuming to administer. Additionally, after infusion, there is a high frequency of headaches and vomiting, suggestive of IVIG-induced aseptic meningitis.

- *Prednisone*: Corticosteroid therapy has been used for many years to treat acute and chronic ITP in adults and children. Prednisolone is given in dose of 1–4 mg/kg/day for 2–4 weeks and then tapered. Platelets usually rise about 3–5 days after steroid initiation, but it can take up to 2 weeks for an effect to be seen. Side effects of steroids include weight gain, irritability, hypertension, and hyperglycemia. Dexamethasone is also given at dose of 20 mg/m<sup>2</sup> over 4 days every for 4–6 courses. Prednisolone appears to induce a more rapid rise in platelet count than in untreated patients with ITP. Corticosteroid therapy is usually continued for short course until a rise in platelet count to  $>20 \times 10^9/L$  has been achieved to avoid the long-term side effects of corticosteroid therapy, especially growth failure, diabetes mellitus, and osteoporosis. The other important modes of steroid action include decreased clearance of opsonized platelets and decreased production of anti-platelet antibodies. Platelet count was observed to recover more rapidly with corticosteroids than with no therapy. Similarly short course of oral prednisolone therapy (4 mg/kg/day for 4 days without tapering) was safe, inexpensive and effective. Efficacy of corticosteroids has been demonstrated in terms of platelet recovery time and not in terms of morbidity or mortality.

Several studies have shown that IV pulse methylprednisolone (30 mg/kg/day for 3 days) is more effective in increasing the platelet count to a safer level.

- *Intravenous anti-D therapy*: For Rh-positive patients, IV anti-D at a dose of 50–75 µg/kg causes a rise in platelet count to  $>20 \times 10^9/L$  in 80–90% of patients within 48–72 hours. When given to Rh-positive individuals, IV anti-D induces mild hemolytic anemia. RBC-antibody complexes bind to macrophage Fc receptors and interfere with platelet destruction, thereby causing a rise in platelet count. IV anti-D is ineffective in Rh-negative patients.

Anti-Rd (D) acts by a mechanism similar to that of IV-IgG. Intravenous (or intramuscular) anti-Rh (D) has been advocated as a cheaper alternative to IV-IgG in Rh (positive) nonsplenectomized patients. It is more effective in acute ITP than in chronic ITP.

Each of these medications may be used to treat ITP exacerbations, which commonly occur several weeks after an initial course of therapy.



In the special case of ICH, multiple modalities should be used, including platelet transfusion, IVIG, high-dose corticosteroids, and prompt consultation by neurosurgery and surgery.

The choice of therapy depends on a variety of factors, including the side effect profile of each agent and the indication for treatment, as well as patient-related factors. Platelet transfusion is generally avoided due to the expected rapid antibody-mediated clearance of transfused platelets and theoretical risk of increased antibody development, but can be used in the management of serious or life-threatening bleeding.

Antifibrinolytic agents (aminocaproic acid and tranexamic acid) can be helpful adjuncts to therapy for mucosal bleeding symptoms. Medications that affect platelet number or function (aspirin, NSAIDs) should be avoided. Activity restrictions may be required depending on the platelet count and bleeding symptoms.

In the case of severe or life-threatening hemorrhage, an aggressive approach with a combination of therapies is warranted. Intravenous immunoglobulin and high-dose IV steroids should be given, with consideration of platelet transfusion/drip to facilitate hemostasis acutely. If the patient has signs and symptoms worrisome for ICH, expeditious imaging should be obtained with surgical and neurosurgical consultations as needed. Urgent/emergent splenectomy can be life-saving in the setting of uncontrolled bleeding or neurologic compromise.

## Splenectomy

The role of splenectomy should be reserved in two occasions, i.e., in older child  $\geq 4$  years with severe idiopathic thrombocytopenic purpura that has lasted longer than 1 year (chronic idiopathic thrombocytopenic purpura) and whose symptoms are not relieved by medical therapy. It is also considered in severe complications such as intracranial hemorrhage.

Results are immediate as platelet antibodies are developed in spleen. Titers of antibodies decrease rapidly after splenectomy. Platelet concentration should be readily available to control excessive bleeding during surgery.

The majority of patients (65–88%) achieve remission immediately after splenectomy. Results of splenectomy are immediate as the antiplatelet antibodies are synthesized in the spleen.

Splenectomy is associated with a lifelong risk of overwhelming postsplenectomy infection caused by encapsulated organisms, increased risk

of thrombosis, and the potential development of pulmonary hypertension in adulthood. As an alternative to splenectomy, rituximab has been used off-label in children to treat chronic ITP. In 30–40% of children, rituximab has induced a partial or complete remission.

## Intracranial Hemorrhage

Intracranial hemorrhage is a life-threatening complication of ITP. Its incidence has been reported to vary from 0.1 to 1%. It was believed that ICH occurs during the first few days of onset of ITP and when the platelet count is less than  $20 \times 10^9/L$ .

The current principle of therapy for ICH is to rapidly increase the platelet count either by splenectomy, platelet transfusions or by IV-IgG. Splenectomy reduces the destruction of both autologous and transfused platelets. About 60–70% of patients sustain permanent remission following splenectomy. Emergency craniotomy is indicated in patients with posterior fossa hemorrhage and progressive neurologic deterioration.

## Chronic ITP

Management of patients with chronic ITP is based on evaluation of the patient's bleeding symptoms, platelet count, overall quality of life, and ability to perform daily activities. Because approximately one-third of patients will have spontaneous remission of their chronic ITP even years after diagnosis, management often consists of observation alone, with pharmacologic intervention reserved for severe thrombocytopenia or bleeding episodes, or before anticipated hemostatic challenges (invasive procedures or high-risk physical activities). However, some children with chronic ITP have more severe thrombocytopenia or significant and frequent bleeding episodes or quality-of-life impairments that necessitate more definitive and durable treatment. Options include rituximab, thrombopoietin receptor agonists, alternative immunosuppressive regimens, and splenectomy. Splenectomy is successful in approximately 70% of children, but concerns over the risk of thrombosis and long-term risk of severe infection, as well as favorable side effect profiles of nonsurgical options, limit its use.

The monoclonal CD20 antibody rituximab has been reported to elicit a complete platelet response for up to a year in 30% of patients with chronic ITP. Infusion reactions, risk of hypogammaglobulinemia and/or infections and very rare risk of progressive multifocal leukomalacia can occur. The thrombopoietin agonist romiplostim



and eltrombopag are efficacious in approximately 70% of children and are increasingly used due to their favorable side effect profiles to and potential for long-term use. These agents work by increasing in platelet production, to compensate for peripheral loss and increase circulating platelet count. Short-term side effects are generally mild and improve with duration of use. Serious side effects are rare and include risk of thrombosis and potential for bone marrow fibrosis. Eltrombopag is an oral agent taken once daily. The dose is weight-

based with a maximum dose of 75 mg. Liver function abnormalities are possible and generally reversible on drug discontinuation. Romiplostim is administered subcutaneously once weekly. The manufacturer recommends weight-based dosing and escalating to a maximum of 10 µg/kg.

*Refractory ITP:* It is not benign. Mortality rate is 5.1%. Drugs used for treatment are vinca alkaloids, cyclophosphamide, azathioprine, cyclosporine, and danazol.

#### THERAPY FOR CHRONIC ITP

##### 1. Blockade of reticuloendothelial system:

- Corticosteroids
  - Standard of high dose
  - Low dose on alternate days
  - Pulse steroids
- IV-IgG
- Anti-Rh (D) globulin
  - Vinca alkaloids (vincristine and vinblastine)
  - Splenectomy
  - Anti-Fc receptor antibody

##### 2. Immunosuppression:

- Cyclophosphamide
- Cyclosporine
- Azathioprine
- Interferons
- Danazol
- Splenectomy

##### 3. Removal of antiplatelet antibodies:

- Plasmapheresis
- Exchange transfusion
- Immunoadsorption

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# Iron Deficiency Anemia

## PRESENTING COMPLAINTS

A 3-year-old boy was brought with the complaints of:

- Repeated attack of cough and cold since 6 months
- Tiredness since 6 months
- On and off pain in the abdomen since 6 months
- Not taking feeds regularly since 1 month

## History of Presenting Complaints

A 3-year-old boy came to the pediatric outpatient department with history of fatigue and repeated attacks of cough and cold since 6 months. According to the mother, her son was getting

repeated chest infections. She also complained that every time he was getting relief only after the administration of antibiotics. She has also noted that her son was becoming pale day by day. Of late, she also noticed that he was not playing with the friends. He was just sitting at one place. He was quite irritable. He was not taking food regularly.

## Past History of the Patient

He was the only child of nonconsanguineous marriage. He was born at term with normal delivery. His birth weight was 3 kg. He cried immediately after the delivery. There was no significant postnatal event. He was discharged on the 5th day. He was on breastfeeds exclusively for 4 months. Weaning was started at 4 months and he was on family food by 15 months. His developmental milestones were normal. Boy had been completely immunized.

### CASE AT A GLANCE

#### Basic Findings

Height	: 90 cm (50th centile)
Weight	: 13 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 110 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 60/40 mm Hg

#### Positive Findings

##### History

- Fatigue
- Repeated respiratory infection
- Pain in abdomen

##### Examination

- Pallor
- Koilonychia
- Bald tongue
- Ejection systolic murmur

##### Investigation

- *Hb*: Decreased
- *ESR*: Raised
- *MCH*: Decreased
- *MCV*: Decreased
- *MCHC*: Decreased
- *Reticulocytes*: Increased
- *Serum iron level*: Decreased

(*ESR*: erythrocyte sedimentation rate; *MCH*: mean corpuscular hemoglobin; *MCV*: mean corpuscular volume; *MCHC*: mean corpuscular hemoglobin concentration)

## EXAMINATION

The boy was moderately built and poorly nourished. He was sitting quietly on the examination table. He was not interested in surroundings. Anthropometric measurements included height was 90 cm (50th centile) and weight was 13 kg (50th centile).

Boy was afebrile. The heart rate was 110 per minute and the respiratory rate was 26 per minute. The blood pressure recorded was 60/40 mm Hg. There was gross pallor and koilonychia was present. There was no lymphadenopathy, no icterus, and no cyanosis.

The tongue was bald. Cardiovascular system revealed the presence of ejection systolic murmur heard at the base. The respiratory system revealed the presence of crepitations at the base of the lungs. The per abdomen examination was normal.

## INVESTIGATION

Hemoglobin	: 6 g/dL
TLC	: 7,900 cells/cu mm
ESR	: 40 mm in the 1st hour

AEC	: 650 cells/cu mm
MCV	: 65 pg
MCH	: 25 pg
MCHC	: 24%
Reticulocyte count	: 3%
Serum iron levels	: 28 µg/dL
Total iron binding capacity	: 360 µg/dL

## DISCUSSION

Iron deficiency is the most common cause of nutritional anemia. Children during the phase of rapid growth such as preschool age and adolescence are at higher risk for development of iron deficiency anemia.

Iron is important in a number of iron dependent enzymes including catalase, peroxidase, cytochromes, and ribonucleotide reductase. It is a major constituent of hemoglobin which is important for oxygen carriage in multicellular organisms.

Term newborns possess about 75 mg of elemental iron/kg (0.25–0.5 g of total body iron), largely acquired during transfer of maternal iron stores during the third trimester of pregnancy. They must then gain 4.5 g of iron over the course of their childhood (1 mg/day) to achieve the nearly 5.0 g of body iron in the average adult. An additional 0.2–0.5 mg/day of absorbed iron is required to balance normal physiologic iron losses.

Most iron in neonate is in circulating hemoglobin. As the relatively high hemoglobin concentration of the newborn infant falls during the first 2–3 months of life, considerable iron is recycled. These iron stores are usually sufficient for blood formation in the first 6–9 months of life in term infants. Stores are depleted sooner in low birth weight infants or infants with perinatal blood loss because their iron stores are smaller. Delayed (1–3 minutes) clamping of the umbilical cord can improve iron status and reduce the risk of iron deficiency, whereas early clamping (<30s) puts the infants at risk for iron deficiency.

Blood loss must be considered as a possible cause in every case of iron deficiency anemia, particularly in older children and adolescents. Chronic iron deficiency anemia from adult bleeding may be caused by a lesion of the gastrointestinal (GI) tract, such as peptic ulcer, Meckel's diverticulum, polyps, hemangioma, or inflammatory bowel disease.

In developing countries, infections with Hookworm, *Trichuris trichiura*, *Plasmodium*, and *Helicobacter pylori* often contribute to iron deficiency.

Celiac disease and giardiasis may interfere with iron absorption.

## PREDISPOSING FACTORS

They are low socioeconomic status with poor hygiene and nutrition, worm infestation; high socioeconomic group with only bottle-feeding and improper weaning and poor breastfeeding; adolescent girls on slimming diet; preterm babies; low birth weight babies born to anemic mother and rapid growth in children.

## IRON SOURCES

It can be divided into two forms of dietary iron: heme iron and non-heme iron. Heme iron is available from meat, fish, and blood products. It is of high bioavailability with 20–30% are absorbed from these foods.

## ETIOLOGY

Iron adequacy is the balance between the iron required on one hand, iron available and absorbed on the other hand. This can be disturbed leading to the deficiency by increased requirement.

### Increased Requirement

Iron requirement is more in infancy, during the period of rapid growth. This makes the full-term prone to deficiency by 4–6 months. In preterm, the deficiency may be seen by 6–8 weeks.

Healthy term infants who are on exclusively breastfeeds are at risk for iron deficiency after they are 6 months old. The lower iron stores of premature infants are more rapidly depleted as compared with term infant.

Breastfed infants require less iron from other food. During the 1st year of life, because of relatively small quantities of iron, it is often difficult to attain sufficient.

Infants who are breastfed exclusively should require iron supplements after 4 months. Increased requirements of iron are more during infancy period of rapid growth. This makes full-term newborn prone to deficiency by 4–6 weeks.

Iron is more required during adolescence, menstruation, pregnancy, and lactation. If the diet is poor or iron is not supplemented, iron deficiency will occur. Low birth weight babies are prone to develop iron deficiency.

### Decreased Availability

Iron availability depends on iron content of diet, type of iron and absorptive capacity of GI tract.

In infancy, breast milk is the main source of iron. Though iron content of breast milk is less, it has high bioavailability. Hence exclusive breast-feeding protects the baby from iron deficiency in first 4–6 months of life. After this, baby needs generous iron supply from proper weaning food. At this stage, bottle-feeding only milk-based diet and improper food habits lead to iron deficiency. Hence proper weaning, breastfeeding and iron supplementation will prevent iron deficiency in infancy.

Only one-tenth of the dietary iron is absorbed by the GI mucosa. Most of the iron is in the ferric form. This is converted into the ferrous form. This is easily absorbed. This conversion is facilitated by hydrochloric acid in the gastric juices. Absorption of iron takes place in the first and second part of the duodenum and at time in jejunum.

The intestinal mucosa controls it. In the normal state, when the iron in the food is in excess, the mucosa holds the iron in the apoferritin in the mucosal cell. This desquamates in 2–3 days and hence getting rid of excess iron.

In the deficiency state, the mucosal cell transports the iron rapidly through the blood circulation. Here it combines with transferrin. It is transported to the site of utilization and storage.

Absorption of iron is decreased by GI tract diseases such as diarrhea, celiac disease, hypoproteinemia, GI surgery, worm infestations, cow's milk allergy, etc. Recurrent infections lead to reduced intake, poor absorption and increase losses due to bleeding.

### Increased Blood Losses

Each mL of packed red blood cell (PRBC) has 1 mg of iron. Hence bleeding can lead to loss of iron from body. Excessive loss of iron can occur due to GI bleeding due to polyps, piles, fissures, Meckel's diverticulum, worms such as hookworms, *T. trichiura*, schistosomiasis, varices, etc.

There could be other forms of chronic blood loss in patients with bleeding disorder. Bleeding as a case of iron deficiency is less common in infancy. It should be thought of in an older child or adult male with unexplained iron deficiency.

Once the iron is assimilated in the body, it is not easily excreted. Average loss of iron per day in children is 0.9 mg/day. 0.6 mg/day is lost in the GI tract in the form of RBCs, bile or exfoliated mucosal cells. The rest is lost from the desquamated cells of the skin and urinary tract.

### PATHOGENESIS

Body iron is predominantly incorporated into the hemoglobin of circulating erythrocytes and their marrow precursors. Phagocytosis of senescent erythrocytes by reticuloendothelial (RE) macrophages and degradation of hemoglobin allow for recovery and recycling of heme iron that provides the majority of the daily iron requirement to the bone marrow. Only a small fraction of the average daily iron requirement is obtained from dietary iron.

In iron-sufficient states, an estimated 10% of dietary iron is absorbed. Therefore, children's diets must contain 10–15 mg of iron to maintain a positive iron balance. During periods of maximal growth-infancy and adolescence-iron requirements for the expanding blood volume and muscle mass may exceed dietary iron accrual, placing those individuals at risk for iron, deficiency. In infancy, particularly when exclusively breastfed, an adequate level of iron intake is difficult to achieve if iron supplementation, iron-fortified formula, or iron-rich foods are not provided.

Some disorders disrupt the integrity of the enteric mucosa and hinder iron absorption. Inflammatory bowel diseases, particularly Crohn's disease and celiac disease, can damage the duodenum, where most iron absorption occurs, and GI bleeding may exacerbate the problem. Children who undergo GI surgery and/or reconstruction may also be at risk for poor iron absorption.

An oral iron challenge can be used to assess iron absorption. This involves obtaining a fasting serum iron level followed by a level 1–2 hours after an oral dose of 1–2 mg/kg of elemental iron, preferably with ferrous sulfate. Failure to observe a marked increase over the baseline level is concerning for iron malabsorption.

Iron homeostasis requires carefully coordinated regulation of intestinal iron absorption, cellular iron import and export, and iron storage. Aside from enterocyte sloughing, humans have no physiologic iron excretion mechanism; therefore, the control of iron balance must occur at the level of intestinal absorption.

Hepcidin, a small peptide hormone synthesized in the liver, plays a central role in iron homeostasis, specifically on intestinal iron absorption and macrophage iron release. It negatively regulates ferroportin, causing its internalization and degradation, thus limiting iron transfer into the plasma. Hepcidin synthesis is decreased in iron-deficient states, allowing for increased ferroportin-mediated cellular iron export and increased iron

absorption and plasma iron levels, and facilitating increased erythrocyte production.

Iron deficiency anemia (IDA) is the end stage of a relatively long drawn process of deterioration in the iron status of an individual. It is only the tip of the iceberg of the iron deficiency state, which may be divided into three functionally distinct stages of severity.

1. *First stage of storage iron depletion:* Iron reserve is smaller or absent. It is characterized by reduced serum ferritin or reduced iron concentration in marrow and liver tissue. Hemoglobin, serum iron transferrin concentration and saturation are within normal limits.
2. *Second stage of iron, limited erythropoiesis:* It is transient and consists of deservied iron transportation. Hemoglobin may still be normal or may be in lower range, but serum iron is low and total iron-binding capacity (TIBC) is increased with normal transferrin saturation and low serum ferritin.
3. *Third stage of iron deficiency anemia:* The flow of iron to erythroid marrow is impaired to cause the reduction in hemoglobin concentration. This leads to progressive microcytic hypochromic anemia, low MCV. Reduced serum iron, transferrin saturation, and serum ferritin levels.

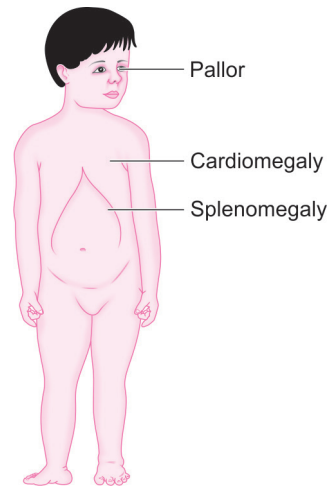
Iron stores in the body such as hemosiderin in the liver and bone marrow are diminished. Thereafter the iron ferritin level falls to less than 10  $\mu\text{g/mL}$  followed by decrease in total iron binding capacity.

Free erythrocyte porphyrin (FEP) level increases. Microcytic hypochromic anemia occurs. Activity of iron containing enzyme diminishes.

Intestinal iron absorption appears to be mediated by at least five physiologic regulators that primarily affect *hepcidin* gene transcription (dietary iron load, total body iron stores, erythropoietic demand, hypoxia, and inflammation), as well as a more recently described erythroid regulator, erythroferrone (ERFE).

## CLINICAL FEATURES (FIG. 1)

Onset may be very insidious and progression of the symptoms and signs may be so gradual that they may not be noticed till hemoglobin drops as low as 3 and 4 g%. However, improved work tolerance and feeling of wellbeing may be noticed following treatment before hemoglobin starts rising. It occurs most frequently between the age of 6 and 24 months and between 11 and 17 years. The peak incidence is at younger age in preterms than in those born at term.



**Fig. 1:** Clinical features.

Symptomatology depends on the rate of fall in hemoglobin and hemostatic adjustment of various systems in the body. In severe IDA, fatigue, shortness of breath, decreased exercise tolerance, irritability, anorexia, pallor may be noted.

Most children with iron deficiency are asymptomatic and are identified by recommended laboratory screening at 12 months of age, or sooner if at high risk. Pallor is the most important clinical sign of iron deficiency but is not usually visible until the hemoglobin falls to 7–8 g/dL. It is most readily noted as pallor of the palms, palmar creases, nail-beds, or conjunctivae.

In mild-to-moderate iron deficiency (i.e., hemoglobin levels of 6–10 g/dL), compensatory mechanisms, including increased levels of 2,3-diphosphoglycerate and a shift of the oxygen dissociation curve, may be so effective that few symptoms of anemia aside from mild irritability are noted.

When the hemoglobin level falls to <5 g/dL, irritability, anorexia, and lethargy develop, and systolic flow murmurs are often heard. As the hemoglobin continues to fall, tachycardia and high-output cardiac failure can occur.

Gradual onset of pallor may escape notice even when hemoglobin falls to 4–5 g%. Blowing apical systolic murmur, recurrent infections, occasionally slightly enlarged spleen are also well known to occur.

Pica is an unexplained but well-documented feature in children with anemia. Habitual craving to eat unusual substance such as dirt, clay (geophagia), ice (pagophagia), laundry starch (amylphagia), salt, cardboard, etc., are seen in almost 70–80% of patients and usually are cured by prompt iron therapy.



The onset of anemia is insidious. Pallor is major sign. The children fail to thrive. They suffer from infection more frequently. Severe anemia leads to cardiac enlargement. Splenomegaly is present. There will be systolic as well as diastolic flow murmur. There will be atrophy of the tongue papillae. Nails become thin, brittle, and flat. Longitudinal ridges appear on nail. Nails become spoon shaped and appear concave—koilonychia. There will be growth retardation. School performance and mental performance will be affected.

Iron deficiency has nonhematologic systemic effects. Both iron deficiency and iron IDA are associated with impaired neurocognitive function in infancy. There is also an association of IDA and later, possibly irreversible, cognitive defects. Given the frequency of iron deficiency and IDA and the potential for adverse neurodevelopmental outcomes, minimizing the incidence of iron deficiency is an important goal.

Growth retardation children with IDA have lower than normal weight at the time of diagnosis, attributable to anorexia, reduced synthesis of nucleic acids and altered intestinal functions. Rapid weight gain usually follows iron therapy.

Epithelial changes koilonychia, platynychia, atrophic glossitis, angular stomatitis, cheilosis, esophageal web (Plummer-Vinson or Paterson-Kelly syndrome), etc., are rare in children and are more common in adults. Koilonychia is the pathognomonic of IDA.

#### ESSENTIAL DIAGNOSTIC POINTS

- Pallor and fatigue
- Poor dietary intake of iron
- Chronic blood loss
- Microcytic hypochromic anemia
- Responds to iron therapy

#### DIAGNOSIS

First, tissue iron stores are depleted. This depletion is reflected by reduced serum ferritin, an iron-storage protein, which provides an estimate of body iron stores in the absence of inflammatory disease. Next, serum iron levels decrease, the iron-binding capacity of the serum (serum transferrin) increases, and the transferrin saturation falls below normal. As iron stores decrease, iron becomes unavailable to complex with protoporphyrin to form heme. Free erythrocyte protoporphyrins accumulate and hemoglobin synthesis is impaired. At this point, iron deficiency progresses to IDA. With less available hemoglobin in each cell, the red cells become smaller and varied in size. The variation in red cell size is measured by an increasing red cell distribution width.

This is followed by a decrease in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH). Developmental changes in MCV require the use of age-related standards for recognizing microcytosis. The RBC count also decreases. The reticulocyte percentage may be normal or moderately elevated, but absolute reticulocyte counts indicate an insufficient response to the degree of anemia. The blood smear reveals hypochromic, microcytic red cells with substantial variation in cell size. Elliptocytic or cigar-shaped red cells are often seen. Detection of increased soluble transferrin receptor and decreased reticulocyte hemoglobin concentration provide very useful and early indicators of iron deficiency; but their availability is more limited.

White blood cell (WBC) count is normal and thrombocytosis is often present. Thrombocytopenia is occasionally seen with iron deficiency, potentially confusing the diagnosis with bone marrow failure disorders. Stool for occult blood should be checked to exclude blood loss as the cause of iron deficiency.

A presumptive diagnosis of IDA is most often made by a complete blood count demonstrating a microcytic anemia with a high red cell distribution width, reduced RBC count, normal white WBC count, and normal or elevated platelet count. Other laboratory studies, such as reduced serum ferritin, reduced serum iron, and increased total iron-binding capacity, are not usually necessary unless severe anemia requires a more rapid diagnosis, other complicating clinical factors are present, or the anemia does not respond to iron therapy. An increase in hemoglobin  $>1$  g/dL after a month of iron therapy is usually the most practical means to establish the diagnosis.

Diagnosis of severe and moderate IDA is relatively straight forward. Low levels of hemoglobin,  $MCV < 75 \mu^3$ ,  $MCH < 28$  Pg, low serum iron and transferrin saturation, and high levels of TIBC and FEP will help diagnose IDA. Red cell distribution width, a parameter available by particle cell counters will be high in IDA.

However, mild case of IDA especially those with hemoglobin concentration within 1 g% below the reference range may be difficult to diagnose. Such children show increase in hemoglobin and feeling of wellbeing when treated with iron.

#### LABORATORY SALIENT FINDINGS

- Decreased serum ferritin
- Decreased transferrin saturation
- Decreased free erythrocyte protoporphyrin
- Decreased hemoglobin
- Decreased MCV

Laboratory test can be divided into test for plasma compartment, test for storage iron, and tests for RBC compartment.

Plasma compartment is tested by doing serum iron, TIBC and TS tests. Storage iron is tested by doing serum ferritin and bone marrow iron staining. RBC compartment is tested by doing blood indices (preferably on particle cell counter) including red cell distribution width (RDW), thorough peripheral smear examination and FEP.

## Screening Tests

The best screening test for the diagnosis of anemia includes measurement of hemoglobin concentration and hematocrit (PCV) in circulating blood. Practically speaking, one can diagnose mild anemia when hemoglobin concentration is below 10 g/dL, moderate anemia between 7 and 10 g, and severe anemia below 7 g%.

## Red Cell Indices

With the availability of electronic particle counters estimation of PCV, MCV, MCH, and RBC count has become accurate and reproducible. Manual determination of these red cell indices is time consuming, variable, and poorly reproducible. Low MCV and MCH favor the diagnosis of IDA.

Reticulocyte is the most recently produced RBC in circulation. The earliest sign of IDA may be fall in concentration of hemoglobin in reticulocyte. The studies have indicated that concentration >30 pg/cell have no chance of IDA.

## Red Cell Distribution Width

Most of the recent particle cell counters give the graph of red cell size distribution and calculated value of the RDW. The variability in size of RBC will lead to a broad base of the graph and increased values of RDW. It reflects the amount of anisocytosis as seen on peripheral smear. In IDA, RBCs have greater anisocytosis and hence, increased value of RDW.

## FREE ERYTHROCYTE PROTOPORPHYRIN

Protoporphyrin accumulates in the RBCs when it does not have sufficient iron to combine with, to form hemoglobin. The free erythrocyte protoporphyrin (FEP) can be measured rapidly by a simple fluorescence assay performed directly on the thin film of blood on hemofluorocytometer. FEP value in a normal person is less than 30–40 µg/dL of RBC. More than 80 µg/dL of RBC below the age of 4 years and >70 mg/dL of RBC above that age are significant values to detect IDA. FEP:Hb ratio is a useful index of iron deficiency. FEP:Hb ratio

increases when iron reserve is exhausted even before anemia becomes apparent.

## Confirmatory Test for IDA

The most commonly used tests for confirming the diagnosis of IDA are serum iron, serum ferritin, and transferrin saturation.

- *Serum iron:* Levels of serum iron reflect the balance between the iron absorbed, iron utilized for hemoglobin synthesis and iron released by red cell destruction and the size of the storage department. Thus, it represents equilibrium between iron entering and leaving the circulation. Serum iron is influenced by many physiological as well as pathological states.
- *Total iron-binding capacity and transferring circulating in the blood:* Normally, there is enough transferrin present in 100 cc of serum to bind about 250–450 µg of iron. TIBC is increased in patients with IDA whereas it is lower in patients with anemia of chronic inflammation as the cause of anemia.
- *Serum ferritin:* Iron is stored in the body in form of ferritin and hemosiderin. Small amount of ferritin is found in blood reflecting the body stores of iron. It is a sensitive measure of total iron stores in the body and can be determined by a radioimmunoassay (RIA) or by the enzyme-linked immunosorbent assay (ELISA). ELISA is a simpler and less expensive method and can be performed on micro quantity of blood. Serum ferritin level less than 10–12 ng/mL indicates depletion of iron stores.
- *Bone marrow examination:* Bone marrow aspiration is not indicated in the diagnosis of IDA. The degree of cellularity and the proportion of myeloid erythroid normoblastic hyperplasia.

### CONFIRMATORY TEST FOR IDA

Age (years)	Serum ferritin (Ng/mL)	Transferrin saturation (%)	RBC FEP (µg/dL)
0.5–4	10	12	80
5–10	10	14	70
11–14	10	16	70
15	12	16	70

### GENERAL FEATURES

- Pagophagia—desire to ingest unusual substance
- Irritability
- Anorexia
- Underweight

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis of microcytic hypochromic anemia include IDA, anemia of chronic infection, thalassemia, sideroblastic anemia, and lead poisoning.

## TREATMENT

The regular response of IDA to adequate amounts of iron is a critical diagnostic and therapeutic feature. Oral administration of simple ferrous salts (most often ferrous sulfate) provides inexpensive and effective therapy.

The therapeutic dose should be calculated in terms of elemental iron. A daily total dose of 3–6 mg/kg of elemental iron in three divided doses is adequate, with the higher dose used in more severe cases. The maximum dose would be 150–200 mg of elemental iron daily. Ferrous sulfate is 20% elemental iron by weight and is ideally given between meals with juice, although this timing is usually not critical with a therapeutic dose.

Parenteral iron preparations are only used when malabsorption is present or when compliance is poor, because oral therapy is otherwise as fast, as effective, much less expensive and less toxic. When necessary, parenteral iron sucrose, ferric carboxymaltose, and ferric gluconate complex have a lower risk of serious reactions than iron dextran, although only the latter is Food and Drug Administration (FDA) approved for use in children.

In addition to iron therapy, dietary counseling is usually necessary. Excessive intake of milk, particularly cow's milk should be limited. Iron deficiency in adolescent girls secondary to menorrhagia is treated with iron and menstrual control with hormone therapy.

If the anemia is mild, the only additional study is to repeat the blood count approximately 4 weeks after initiating therapy. At this point, the hemoglobin has usually risen by at least 1–2 g/dL and has often normalized. If the anemia is more severe, earlier confirmation of the diagnosis can be made by the appearance of a reticulocytosis usually within 18–96 hours of instituting treatment. The hemoglobin will then begin to increase 0.1–0.4 g/dL per day depending on the severity of the anemia. Iron medication should be continued for 2–3 months after blood values formalize to reestablish iron stores. Good follow-up is essential to ensure a response to therapy.

Because a rapid hematologic response can be confidently predicted in typical iron deficiency, blood transfusion is rarely necessary. It should only be used when heart failure is imminent or if

the anemia is severe with evidence of substantial ongoing blood loss. Unless there is active bleeding, transfusions must be given slowly to avoid precipitating or exacerbating congestive heart failure.

*Treatment of cause:* It is important to find out the etiological factor of iron deficiency to prevent failure of therapy and recurrence of deficiency after treatment is stopped. Promotion of exclusive breastfeeding for first 4–6 months, continuing breastfeeds for as long as possible thereafter with introduction of proper and age appropriate food items and prophylactic iron supplementation will prevent iron deficiency during infancy and early child. In older children, diet modification to improve total calories intake and iron containing food will prevent iron deficiency. Treatment of worms, giardiasis, bleeding from any sites, recurrent infections is must to treat the patient adequately.

*Iron supplementation:* Iron can be given orally or parenterally.

## Oral Iron Therapy

Oral iron therapy is cost-effective, safe, convenient, well tolerated, preferred and advocated route of therapy.

### Dose

It is given in the dose of 4–6 mg, of elemental iron/kg/day. It is ideally given as single dose in older children or in two divided doses in younger children. It is preferably given in between meals to facilitate better absorption. Compliance in the 1st month of therapy is important as majority of iron absorption occurs during this period. It is continued for at least 2–3 months after hemoglobin becomes normal to replenish stores.

Various iron salts available include ferrous fumarate, ferrous gluconate, ferrous sulfate-hydrous or anhydrous forms, ferric salts, ferrous glycine sulfate, and iron polymaltose complexes. Of these ferrous salts are preferred as they are better absorbed than ferric forms. Ferrous sulfate is the best as it is also cost effective.

Nausea, vomiting, abdominal cramps, diarrhea, constipation, straining of tongue and teeth, blackish discoloration of stools, etc., are common side effects.

## Parenteral Iron Therapy

### Indications:

- Intolerance oral iron
- Malabsorptive states
- Ongoing blood loss

This includes both intramuscular (IM) and intravenous (IV) iron therapy. The preparation available is iron dextran which is a complex of ferric hydroxide with high molecular weight dextrans in a colloidal solution containing 50 mg of elemental iron/mL.

### Dose

Total dose of elemental iron (mg) = wt. (kg) × Desired increment of Hb (g/dL) × 3  
OR

Iron required (mg) = wt. (kg) × 2.3 × (15 – patients Hb in per dL) + (500 to 1000 mg) is given in divided doses IM or as full-dose IV therapy.

- **Intramuscular route:** This is very painful and may lead to serious allergic reactions and hence not used in children. IM injections are best given into the upper outer quadrant of gluteal region using Z-track technique. A dose of 0.1 mL should be given as test dose intramuscularly, and if there are no reactions within 1 hour, full dose (to a maximum of 0.5 cc) can be given every day.
- **Intravenous route:** There are two methods: infusion of total dose diluted in ration of 5 mL of iron dextran complex in 100 mL of normal saline. Initially, flow rate should be kept at 20 drops/min for 5–10 minutes and if there are no reactions, then rate can be increased to 40–60 drops/min.
- **Bolus injection of iron dextran:** Bolus of iron dextran diluted in 20 mL of saline is given over 10–20 minutes.

Both these routes are, however, used after a prior sensitivity testing where 1 mL of iron dextran solution is diluted in 20 cc of normal saline and injected slowly over 10–15 minutes following which one should observe for reactions for ½–1 hour.

Time after iron administration	Response
12–24 hours	Replacement of intracellular iron enzymes; subjective improvement; decreased irritability; increased appetite
36–48 hours	Initial bone marrow response; erythroid hyperplasia
48–72 hours	Reticulocytosis; peaking at 5–7 days
4–30 days	Increase in hemoglobin level
1–3 months	Repletion of stores

**Side effects:** Reactions can occur with both IM and IV therapy and can be either immediate or delayed.

- **Immediate reactions:** These include pain at the injection site, flushing, and metabolic taste.

Such reactions are brief in duration and often are relieved by slowing the rate of injection. Severe reactions such as anaphylaxis, hypotension, cardiac arrest, headache, malaise, vomiting, nausea, etc., should be contraindication to further doses.

- **Delayed reactions:** These include tender regional lymphadenitis, myalgia, arthralgia, fever, etc.

Though most of the reactions are mild and transient. Anaphylactic reactions may be life-threatening and hence one should always keep injection adrenaline and hydrocortisone, and resuscitative measures handy before injecting. Parenteral therapy should be only given in a hospital setup.

### PREVENTION

Iron deficiency is best prevented to avoid both its systemic manifestations and the anemia. Breastfeeding should be encouraged, with the addition of supplemental iron at 4 months of age. Infants who are not breastfed should only receive iron-fortified formula (12 mg of iron/L) for the 1st year, and thereafter cow's milk should be limited to >20–24 oz daily. This approach encourages the ingestion of foods richer in iron and prevents blood loss as a result of cow's milk-induced enteropathy.

When these preventive measures fail, routine screening helps prevent the development of severe anemia. Routine screening using hemoglobin or hematocrit is done at 12 months of age, or earlier if at 4 months of age the child is assessed to be at high risk for iron deficiency. Thereafter, screening should continue if risk factors are identified.

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## PRESENTING COMPLAINTS

A 5-day-old girl baby was brought with the complaints of:

- Breathlessness since 1 day
- Irritability since 6 hours
- Excessive crying since 2 hours

## History of Presenting Complaints

A 5-day-old girl baby was brought to the hospital with history of irritability, excessive crying and breathlessness. The mother also said that her daughter was not taking feeds regularly. There was also a history of subcostal indrawing. But there was no history of cough and cold, suggestive of respiratory tract infection. There was no history of vomiting and loose motion. Child used to become silent on taking into the mother's lap.

## Past History of the Patient

She was the first sibling of nonconsanguineous marriage. The mother was hypertensive antenatally.

But the blood pressure was under control with antihypertensive medicine. She was delivered at term by normal vaginal delivery. She cried immediately after the delivery. Cry of the baby was normal. Features of intrauterine growth retardation (IUGR) were present. Birth weight was 3 kg. There was no significant postnatal event. The baby was taking breast milk and was discharged on the 3rd day.

## EXAMINATION

On examination, the child was irritable. Features of IUGR were present. The child used to be more comfortable on mother's lap. Anterior fontanelle was normal. Ear was normal. Anthropometric measurements included the length was 45 cm (<3rd centile), the weight was 2.75 kg (>10th centile) and the head circumference was 34 cm.

The child was afebrile, the heart rate was 128 per minute, and the respiratory rate was 48 per minute. The blood pressure recorded was 50/40 mm Hg. Subcostal indrawing was present.

The child looked more plethoric than normal. Icterus was present. There was no clubbing and lymphadenopathy. The cardiovascular examination revealed tachycardia and no murmur. Per abdomen examination revealed presence of the hepatomegaly about 4 cm below the costal margin. It was tender and soft in consistency. Bowel sounds were regular.

## INVESTIGATION

Hemoglobin	: 22 g/dL
TLC	: 7,600 cells/cu mm
Platelet count	: 250,000 cells/cu mm
Red cell count	: $8.0 \times 10^6$ cells/cu mm
PCV	: 60%
Serum bilirubin	: 3 mg/dL
Coombs' test	: Negative
Blood group	: O-positive
Peripheral blood smear	: Normal
CSF examination	: Normal
X-ray chest	: Normal

### CASE AT A GLANCE

#### Basic Findings

Length	: 45 cm (<3rd centile)
Weight	: 2.75 kg (>10th centile)
Temperature	: 37°C
Pulse rate	: 128 per minute
Respiratory rate	: 48 per minute
Blood pressure	: 50/40 mm Hg

#### Positive Findings

##### History

- Irritability
- Respiratory distress
- Hypertension in mother

##### Examination

- Intrauterine growth retardation
- Plethoric child
- Tachypnea
- Tachycardia
- Tender hepatomegaly

##### Investigation

- Hemoglobin: Increased
- PCV: Increased



## DISCUSSION

Polycythemia vera is also called polycythemia rubra vera, or erythemia, or vague Osler disease.

Polycythemia is defined by the venous hematocrit of 65%, because this exceeds the hematocrit found in normal newborn by two standard deviation. As the central venous hematocrit raises above 65%, there is dramatic increases in viscosity. Because direct measurement of blood viscosity is not available, high hematocrit level is the best indirect indicator of hyperviscosity.

The fundamental abnormality is hyperplasia of precursor of red cells, granulocytes and platelets in bone marrow. This results in excess of these cells in peripheral blood.

Monozygotic twins with placental vascular anastomoses may have unequal distribution. Hence one twin is born pale and with hypovolemia, while other is plethoric. Neonatal polycythemia is more common with Down syndrome, Beckwith's syndrome, IUGR, and small-for-date (SFD) babies.

Polycythemia exists when the red blood cell (RBC) count, hemoglobin level, and total RBC volume all exceed the upper limits of normal. In postpubertal individuals, an RBC mass >25% above the mean normal value (based on body surface area) or a hemoglobin >18.5 g/dL (in males) or >16.5 g/dL (in females) indicate absolute erythrocytosis.

A decrease in plasma volume, such as occurs in acute dehydration and burns, may result in a high hemoglobin value. These situations are more accurately designated as hemoconcentration or relative polycythemia because the RBC mass is not increased and normalization of the plasma volume restores hemoglobin to normal levels. Once the diagnosis of true polycythemia is made, sequential studies should be done to determine the underlying etiology.

Polycythemia vera is an acquired clonal myeloproliferative disorder. Although primarily manifesting as erythrocytosis, thrombocytosis and leukocytosis can also be seen. When isolated severe thrombocytosis exists is the absence of erythrocytosis, the myeloproliferative disorder is called essential thrombocythemia. The erythropoietin receptor is normal, and serum erythropoietin levels are normal or low. *In vitro* cultures do not require added erythropoietin to stimulate growth of erythroid precursors. Risk factors for development of polycythemia vera include a family history of polycythemia vera and presence of an autoimmune disorder such as Crohn's disease.

Secondary polycythemia results either because of hypoxia or without hypoxia. Hypoxia may be due

to underlying disease. The most common diseases are pulmonary and cardiac disease. The infants are associated with cyanosis and clubbing with engorged retinal vessels. Secondary polycythemia without hypoxia is associated with renal disorders and tumor. This is due to increased erythropoietin production.

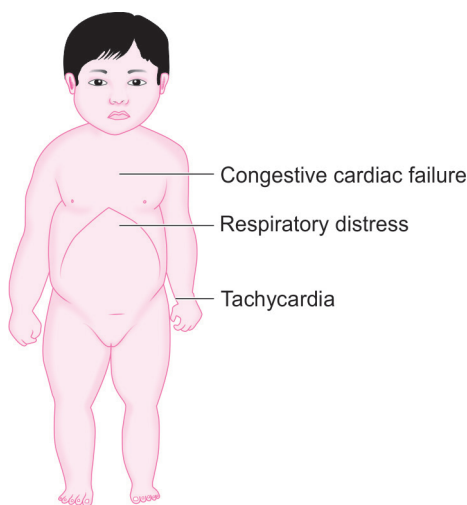
## CLINICAL FEATURES (FIG. 1)

The clinical picture is influenced by increased blood volume, and also by thrombotic and hemorrhagic complication. Increased blood volume produces engorgement and slowing of the circulation in many organs, and symptoms may be referred to number of system.

Patients with polycythemia vera usually have hepatosplenomegaly. Erythrocytosis may cause hypertension, headache, shortness of breath, neurologic symptoms and increases the risk of thrombosis. Granulocytosis may cause diarrhea or pruritus from histamine release. Thrombocytosis (with or without platelet dysfunction) may cause thrombosis or hemorrhage.

The infant may present with convulsion, respiratory distress, tachycardia, congestive cardiac failure and hyperbilirubinemia. These may be associated with hypoglycemia and hypocalcemia.

Cardiovascular defects involving right to left shunt and pulmonary disease interfering with the proper oxygenation. These are the most common causes of hypoxic polycythemia. Clinical findings usually include cyanosis, hyperemia of the sclera and mucus membrane and clubbing of the fingers. As the hematocrit rise above 65%,



**Fig. 1:** Clinical features.

clinical manifestation of the hyperviscosity such as headache and hypertension occur.

## CONGENITAL POLYCYTHEMIA

Life-long or familial polycythemia should trigger a search for a congenital problem. These inherited conditions may be transmitted as dominant or recessive disorders. Autosomal dominant causes include hemoglobin that have increased oxygen affinity [P50 (partial pressure of oxygen in the blood at which the hemoglobin is 50% saturated) <20 mm Hg], erythropoietin receptor mutations resulting in an enhanced effect of erythropoietin or mutations in the von Hippel-Lindau gene that result in altered intracellular oxygen sensing. Another rare cause is autosomal recessive 2,3-diphosphoglyceric acid deficiency, which leads to a left shift of the oxygen dissociation curve, increased oxygen affinity, and consequent polycythemia.

Subtle decreases in oxygen delivery to tissues may cause polycythemia. Congenital methemoglobinemia resulting from an autosomal recessive deficiency of cytochrome b5 reductase may cause cyanosis and polycythemia. Most affected individuals are asymptomatic. Neurologic abnormalities may be present in patients whose enzyme deficits are not limited to hematopoietic cells. Hemoglobin M disease (autosomal dominant) causes methemoglobinemia and can lead to polycythemia. Cyanosis may occur in the presence of as little as 1.5 g/dL of methemoglobin but is uncommon in other hemoglobin variants unless hyperviscosity results in localized hypoxemia.

## ACQUIRED POLYCYTHEMIA

Polycythemia may be present in clinical situations associated with chronic arterial oxygen desaturation. Cardiovascular defects involving right-to-left shunts and pulmonary diseases interfering with proper oxygenation are the most common causes of hypoxic polycythemia. Clinical findings usually include cyanosis, hyperemia of the sclerae and mucous membranes, and clubbing of the fingers. As the hematocrit rises to >65%, clinical manifestations of hyperviscosity, such as headache and hypertension, may require phlebotomy. Living at high altitudes also causes hypoxic polycythemia; the hemoglobin level increases approximately 4% for each rise of 1,000 m in altitude. Partial obstruction of a renal artery rarely results in polycythemia. Polycythemia has also been associated with benign and malignant tumors that secrete erythropoietin. Exogenous or

endogenous excess of anabolic steroids also may cause polycythemia. A common spurious cause is a decrease in plasma volume such as in moderate-to-severe dehydration.

## WHO DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA

### Major Criteria

1. Hemoglobin (Hb) > 18.5 g/dL (men) or Hb >16.5 g/dL (women)  
Or  
Hb or hematocrit (Hct) > 99th percentile of reference range for age, sex, or altitude of residence or elevated red cell mass >25% above mean normal predicted value.  
Or  
Hb > 17 g/dL (men) or Hb > 15 g/dL (women) if associated with a sustained increase of 2 g/dL from baseline that cannot be attributed to correction of iron deficiency.
2. Presence of *JAK2* or similar mutation.

### Minor Criteria

1. Bone marrow trilineage myeloproliferation
2. Subnormal serum erythropoietin level
3. Endogenous erythroid colonies (EEC) growth

## DIAGNOSIS

Both major criteria and one minor criterion or first major criterion and two minor criteria are required for diagnosis.

The overproduction of the red cells is responsible for symptoms. This along with excess number of platelets is the cause of vascular thrombosis. This causes much of morbidity and mortality. It exists when the red cell count, the hemoglobin level and total RBC volume exceed the upper limit of the normal.

Measurement of total RBC volume by radioisotopic technique is essential for differential diagnosis of polycythemia.

True polycythemia is characterized by increase of both RBC and total blood volume. Supportive laboratory abnormalities are thrombocytosis (>400.00/ $\mu$ C) leukocytosis, i.e., 1200/ $\mu$ L), increased leukocyte phosphatase level >100  $\mu$ L and increased vitamin B<sub>12</sub> (>900 pg/mL).

High levels of hemoglobin and hematocrit are usual in the newborn. The normal hemoglobin at birth is 14–21 g/dL and hematocrit is 45–65%. The blood volume of the normal term infant is 70–100 mL/kg and red cell volume is 40–60 mL/kg. In polycythemia, the red cell count is increased

and hematocrit is increased to more than 60%. The hemoglobin level and ESR are also increased. White cell count may be normal or raised. It will be raised in polycythemia rubra.

#### ESSENTIAL DIAGNOSTIC POINTS

- *CNS*: Lethargy, hypotonia, irritability, seizures
- *GIT*: Vomiting, distension, NEC
- *Renal*: Renal vein thrombosis, acute renal failure
- *Cardiopulmonary system*: Respiratory distress, congestive cardiac failure
- Hypoglycemia
- Increase in both RBCs and total blood volume
- Hyperplasia of precursor of red cells, granulocytes, and platelets in bone marrow
- Phlebotomy, partial exchange transfusion

#### LABORATORY SALIENT FINDINGS

- Increased hemoglobin
- Increased Hematocrit
- Increased red cell count
- Increased ESR

Complications include bleeding, thrombosis, myelofibrosis and acute leukemia.

#### GENERAL FEATURES

- Convulsions
- Hyperbilirubinemia
- Hypoglycemia
- Hypocalcemia

### TREATMENT

Partial exchange transfusion can be performed through the umbilical venous catheter, an umbilical artery catheter, or a peripheral venous catheter. Aliquots of 5% of estimated blood volume are withdrawn and replaced either with fresh frozen plasma or normal saline. The amount of the blood volume to be replaced is calculated as follows:

$$\text{Blood volume to be exchanged} = \frac{\text{Observed hematocrit} - \text{Dissolved hematocrit}}{\text{Observed hematocrit} \times \frac{\text{Blood volume} \times \text{Weight (kg)}}{\text{Weight (kg)}}}$$

For mild disease, observation is sufficient. When the hematocrit is >65–70% (hemoglobin >23 g/dL), blood viscosity markedly increase. Periodic phlebotomy may prevent or decrease symptoms such as headache, dizziness, or exertional dyspnea. Apheresed blood should be replaced with plasma or saline to prevent hypovolemia in patients accustomed to a chronically elevated total blood volume. Increased demand for red blood cell production may cause iron deficiency. Iron deficient microcytic red cells are more rigid, further increasing the risk of intracranial and other thromboses in patients with polycythemia. Periodic assessment of iron status, with treatment of iron deficiency, should be performed.

In symptomatic children, phlebotomy is aliquots of 10–15 mL/kg replaced with equal volume of plasma or normal saline may be indicated to reduce the red cell mass and hyperviscosity. If required antiproliferative chemotherapy is considered.

Phlebotomy is the initial treatment of choice to alleviate symptoms of hyperviscosity and decrease the risk of thrombosis. Iron supplementation should be given to prevent viscosity problems from iron-deficient microcytosis or thrombocytosis. In patients with marked thrombocytosis, antiplatelet agents (e.g., aspirin) may reduce the risks of thrombosis and bleeding. If these treatments are unsuccessful or the patient has progressive hepatosplenomegaly, antiproliferative treatments (hydroxyurea, anagrelide, interferon- $\alpha$ ) may be helpful. The use of JAK2 inhibitors is an active area of investigation. Transformation of the disease into myelofibrosis or acute leukemia is rare in children. Prolonged survival is not unusual.

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# Sickle Cell Anemia

## PRESENTING COMPLAINTS

A 4-year-old boy was brought with the complaints of:

- Severe backache since 1 day
- Vomiting since 1 day

## History of Presenting Complaints

A 4-year-old boy was brought to the pediatric casualty with history of severe backache and vomiting since previous night. Backache was present in the lower back. It was very much severe, that boy was finding very difficult to get up from the sitting posture. Along with that the child had vomiting. Vomiting was projectile in nature. The child had vomited all the food he had taken in night. Vomiting remained uncontrolled. Child was not tolerating any food and not even the water.

Mother gave history of similar type of attack of backache occurred during the preceding months. He was admitted in the hospital for this purpose.

### CASE AT A GLANCE

#### Basic Findings

Height	: 100 cm (50th centile)
Weight	: 15 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 100 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 100/70 mm Hg

#### Positive Findings

##### History

- Backache
- Vomiting
- Repeated episodes

##### Examination

- Pallor
- Splenomegaly

##### Investigation

- Hemoglobin: Decreased
- Peripheral blood smear: Target cells, sickled cells, nucleated red blood cells, hypochromic microcytic anemia
- X-ray skull: Hair on end appearance of frontal bone

Intravenous (IV) fluids, analgesics, and antibiotics were given.

## Past History of the Patient

He was the first sibling of non-consanguineous marriage. He was born at full term and delivered vaginally. He cried immediately after birth. There was no significant postnatal event. Child was exclusively breastfed for 3–4 months. Weaning started with cereals and fruits. His developmental milestones were normal. He had been completely immunized. His backache and vomiting was the main concern of the parents.

## EXAMINATION

The boy was moderately built and nourished. He appeared pale and apprehensive. Anthropometric measurements included height was 100 cm (50th centile) and weight was 15 kg (50th centile).

The boy was febrile. The pulse rate was 100 per minute and the respiratory rate was 20 per minute. The blood pressure recorded was 100/70 mm Hg. Pallor and icterus were present. There was no lymphadenopathy and no cyanosis.

Per abdomen examination revealed the enlarged spleen about 3 cm below the costal margin. It was nontender and firm in consistency. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 7 g/dL
TLC	: 11,200 cells/cu mm
ESR	: 29 mm in the 1st hour
Peripheral blood smear	: Shows hypochromic microcytic anemia, elongated crescent-shaped red blood cells and target cells
AEC	: 400 cells/cu mm
Serum bilirubin	: 2 mg/dL
X-ray skull	: Showed hair on end appearance of the frontal bone
X-ray chest	: Normal

## DISCUSSION

An anemic child presented with history of backache and vomiting. There were repeated attacks of backache in the last few months. On examination, the child had mild splenomegaly. Radiograph of the skull showed hair on end appearance. All these go in favor of sickle cell crisis which is a part of sickle cell anemia.

It is an inherited disorder. In heterozygous state of sickle cell trait, only one mutant chain is inherited. Amino acid sequence in the  $\beta$ -peptide chain is abnormal. On the beta chain, valine is substituted for glutamic acid at position 6. The alpha chain is normal. This results in sickle hemoglobin.

Sickle cell disease (SCD) is the name for a group of related disorders caused by sickle hemoglobin (HbS). HbS is qualitatively abnormal hemoglobin caused by a point mutation of the  $\beta$ -globin gene. The sixth codon of the normal  $\beta$ -globin gene, GAG, codes for glutamic acid. In HbS, the adenine nucleotide is replaced by thymidine, producing GTG, which is a codon for valine.

## PATHOPHYSIOLOGY

Hemoglobin S (HbS) is the result of a single base-pair change, thymine for adenine, at the sixth codon of the  $\beta$ -globin gene. This change encodes valine instead of glutamine in the sixth position in the  $\beta$ -globin molecule, sickle cell anemia (HbSS), homozygous HbSS, occurs when both  $\beta$ -globin alleles have the sickle cell mutation (beta's). The glutamine-to-valine substitution replaces a hydrophilic glutamic acid with a hydrophobic valine, permitting abnormal hydrophobic interactions between adjacent deoxyhemoglobin molecules, which decreases the solubility of HbS in the deoxygenated state. Thus, as sickled red blood cells (RBCs) traverse the circulation, cycling through oxygenated and deoxygenated states, HbS repeatedly forms rigid polymers that damage the RBC membrane, causing a hemolytic anemia and, ultimately, the systemic manifestations of SCD.

Sickle cell disease refers to not only patients with sickle cell anemia, but also to compound heterozygotes where one  $\beta$ -globin allele includes the sickle cell mutation and the second  $\beta$ -globin allele includes a gene mutation other than the sickle cell mutation, such as HbC,  $\beta$ -thalassemia, HbD, and HbO. In sickle cell anemia, HbS is commonly as high as 90% of the total hemoglobin; whereas as in SCD, HbS is >50% of total hemoglobin.

As they traverse the circulation, RBCs that contain mostly HbS go through cycles of sickling

(polymerization of HbS) and unsickling (depolymerization of HbS) due to deoxygenation of HbS in the tissues and reoxygenation in the lungs. The tendency of individual RBCs to sickle is influenced by several factors including the relative concentration of HbS in the cell, the abundance of other hemoglobins that inhibit the polymerization of deoxy-HbS (notably HbF), and the degree to which the HbS is deoxygenated. When a solution of HbS is deoxygenated, there is a characteristic time delay during which no polymerization occurs, followed by a phase of rapid polymerization. In vivo, this delay allows most HbS-containing RBCs to traverse the capillary beds before polymerization and sickling occur; small number of RBCs remain permanently sickled due to membrane damage, even when fully oxygenated. These are called irreversibly sickled cells. Hemoglobins such as F and A within the RBC inhibit or delay the polymerization of HbS.

In RBCs, the hemoglobin molecule has a highly-specified conformation allowing for the transport of oxygen in the body. In the absence of globin-chain mutations, hemoglobin molecules do not interact with one another. However, the presence of HbS results in a conformational change in the hemoglobin tetramer and, in the deoxygenated state, HbS molecules can now interact with each other forming rigid polymers that give the RBC its characteristic "sickled" shape. The lung is the only organ capable of reversing the polymers, and any disease of the lung can be expected to compromise the degree of reversibility.

Intravascular sickling primarily occurs in the postcapillary venules and is a function of both mechanical obstruction by sickled RBCs and increased adhesion between RBCs, leukocytes and the vascular endothelium. SCD is also an inflammatory disease based on nonspecific markers of inflammation.

Hemoglobin is normally present in soluble form in the red blood corpuscle. The tendency of deoxyhemoglobin S to undergo polymerization is responsible for innumerable expressions of the sickling syndromes. The 'sol' form of hemoglobin changes to 'gel' form when HbS is deoxygenated. In gel form the hemoglobin changes to small, rigid, boat shaped objects known as "tactoids." These tactoids polymerize and form a helical structure with 14–16 tetramers in each layer. The points of contact between tactoids are along the longitudinal axis and laterally between the chains.

Sickle erythrocytes become dehydrated over time through loss of potassium and water, and this enhances polymerization of HbS. The renal



medulla is especially susceptible to damage from sickling because its hypertonicity further promotes polymerization of HbS. The spleen and bone marrow are similarly prone to damage because their sluggish blood flows allow more time for deoxygenation and polymerization of HbS to occur in capillaries and sinusoids.

The two main pathophysiologic consequences of polymerization of S, or sickling, are hemolysis and vaso-occlusion. Hemolysis or destruction of RBCs, in SCD occurs predominantly in the extravascular compartment. Cycles of sickling damage the RBC, especially its membrane. These damaged RBCs are recognized as abnormal and removed from circulation by the reticuloendothelial system.

Some intravascular hemolysis occurs as well, by microvascular trapping and destruction of adhesive and rigid sickle RBCs. The mean RBC lifespan in HbSS is dramatically shortened to 10–20 days from the normal RBC lifespan of 120 days. The rate of hemolysis in SCD usually exceeds the rate at which new RBCs can be produced by the bone marrow. Therefore, SCD is characterized by a partially compensated hemolytic anemia with significant reticulocytosis.

*The two major pathophysiological mechanisms include:*

1. **Hemolysis:** Sickled RBCs undergo both intravascular and extravascular hemolysis. This leads to anemia, reticulocytosis, jaundice, gallstones, and occasional aplastic crisis.
2. **Vaso-occlusive:** Intermittent and chronic vaso-occlusion results in both acute exacerbation (e.g., painful crisis and stroke) and chronic disease manifestation (e.g., retinopathy, renal disease). The adhesion of sickled erythrocytes to inflamed vascular endothelium is the principle pathological component.

Normally during oxygenation in the lungs the  $PO_2$  is 95 torr. When oxygenated RBCs enter arterioles and capillaries in the tissues, the  $O_2$  is released to the tissues. In venous blood  $PO_2$  drops to 40 torr. The equilibrium of HbS between sol and gel form is affected by  $O_2$  tension, concentration of deoxyhemoglobin in RBC, p2,3-DPG, temperature and presence of other hemoglobin.

Ionic changes HbS polymerization is associated with decrease in potassium, increase in sodium, and increase in calcium content of red cell. Loss of potassium and gain of sodium is due to partial failure of ATPase pump, which regulates Na and K transport.

In addition to their shortened lifespan, sickle erythrocytes are also abnormally adhesive and

have decreased flexibility. Consequently, they can adhere to and damage the endothelium of blood vessels and block the flow of blood. This microvascular obstruction, called vaso-occlusion, leads to ischemia and interaction of different tissues. Vaso-occlusion is believed to be the main cause of acute episodes of pain that are characteristic of SCD.

Finally, SCD is also characterized by an as-yet incompletely understood vasculopathy caused by endothelial activation, abnormal interactions between the endothelium and blood cells, and reduced nitric oxide (NO) signaling. Vascular intimal proliferation results in progressive narrowing of the vessel lumen, constraining perfusion of downstream tissues. This progressive stenosis, in conjunction with chronic anemia and episodic vaso-occlusion, is responsible for the chronic organ damage seen in people with SCD.

## Change in RBC Membrane

The membrane damage is pronounced with repeated cycles of sickling and unsickling, resulting in fixation of membrane in sickled configuration leading to irreversible sickle cell formation.

Heinz bodies are aggregates of small amount of sickle hemoglobin form micro-Heinz bodies. This gets attached to cytoplasmic part of band 3 protein of red cell membrane. This binding results in changes on outer side of membrane forming antiband 3 protein antibodies contributing to shortened lifespan of “SS” red cells.

Increased adherence to endothelium in sickle cell disease red cells have tendency of binding endothelium. This is probably due to surface molecule receptors vascular cell adhesion molecule, and fibronectin. The red cells adhere to endothelium, assume sickle shape after deoxygenation and damage the endothelial cells leading to subendothelial infiltration and narrowing of the vessels. Platelets aggregate over the adherent red cells and damaged endothelium, causing blockage of microvasculature and ischemia of the tissue.

Homozygous state causes the sickle cell disease. It is characterized by episodes of pain and sickled RBCs and crisis. The types of crisis include vaso-occlusive crisis, anoxic crisis and hemolytic crisis.

Under the conditions of anoxia and acidosis, the erythrocytes are deformed into sickle-shaped cells. These distorted cells block the capillaries and cause local anoxia. Anoxia leads to further sickling. This produces the blockage of the capillaries. It causes infarction in various tissues and organs.

Hyperhemolytic crisis occurs in homozygous sickle cell disease which co-incidentally has G6PD deficiency, which ingests the oxidant drug.

Other states such as vomiting, diarrhea, fever produce hemoconcentration and precipitate into sludging. The sickle cell sequestered in the capillaries of reticuloendothelial system are hemolyzed. The resulting anemia is associated with reticulocytes. Biliary pigment stones, gallstones are formed in long standing cases. Hypoxia produces clubbing. Anemia leads to hyperactivity of bone marrow resulting in radiological change in bone.

Microinfarcts in the liver cause hepatomegaly and jaundice. Infarct in the spleen manifests as abdominal pain with eventual fibrosis and reduction in the spleen size.

Central nervous system infarct occurs proceeding strokes. Renal function is progressively impaired by diffuse glomerular and tubular fibrosis. Renal papillary necrosis and nephrotic syndrome occur.

Functional asplenia may begin as early as 5–6 months of age. It may precede the presence of Howell–Jolly bodies in the peripheral smear. Most children with HbSS who are more than 5 years old have functional asplenia with the small atrophied spleen. Splenic dysfunction causes increased susceptibility to meningitis and sepsis.

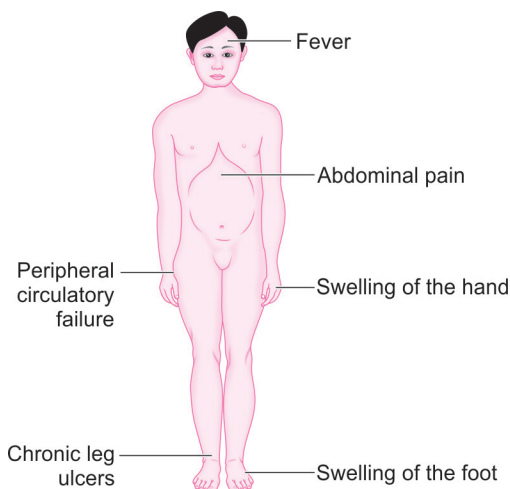
### Sickle Cell Trait

The predominance of HbA within HbS trait, RBCs prevents sickling under normal oxygen tensions. The hypertonicity and relative acidosis in the renal medulla can induce sickling in the kidney. Therefore, hyposthenuria and renal papillary necrosis with gross hematuria are known potential medical complications of HbS trait. Under conditions of extreme physical exertion, low oxygen tension, or both, other complications have been described in people with HbS trait.

It is important for individuals to know that they have HbS trait because of the risk to their offspring. Sickle cell anemia is an autosomal recessive disease, so if both parents have HbS trait, each of their offspring will have a 25% chance of having HbSS. Even if only one parent has HbS trait, offspring are still at risk of having SCD if the parent without HbS trait happens to have HbC trait or  $\beta$ -thalassemia trait.

### CLINICAL FEATURES AND RESPECTIVE MANAGEMENT (FIG. 1)

There are considerable variations in the manifestations of SCD. Some patients remain a symptomatic



**Fig. 1:** Clinical features.

and are detected only during screening, whereas others constantly experience painful episodes. Most of the patients fall in these two extreme categories and experience intermittent clinical crisis.

### CLINICAL COURSE

A patient with SCD has at baseline a chronic hemolytic anemia to which he or she becomes physiologically adapted. This baseline anemic, but relatively healthy, state is called the steady state. This steady state is punctuated by intermittent, acute episodes of illness, called vaso-occlusive episodes, events, or crises, though the term crisis. Recurrent vaso-occlusion and chronic anemia also produce chronic organ damage.

At birth, newborns with HbSS disease have normal birth weight and are not anemic. Anemia and reticulocytosis usually appear between 2 and 6 months of age. Scleral icterus and a cardiac flow murmur are expected findings as a result of the anemia. Prophylactic penicillin to prevent pneumococcal sepsis should be initiated prior to the onset of splenic infarction and hyposplenism, which may begin to occur as early as 3 months of age. Before splenic infarction is complete, the spleen may be palpably enlarged.

Acute vaso-occlusive events are unusual before 6 months of age.

The first painful event is often dactylitis, which is a swelling of the hands and feet caused by vaso-occlusion in the marrow found in the bones of the digits. Dactylitis is rare beyond 3 years of age once this marrow is resorbed. Although birth weight is normal, growth retardation is commonly observed during childhood. On average, individuals with

HbSS tend to be thinner and shorter than their peers, but a normal adult height can often be attained. The onset of puberty and development of secondary sex characteristics are usually delayed by 2–3 years.

Usually children with sickle cell disease are asymptomatic up to 6 months of age. This is due to large amount of hemoglobin F at birth, which has a positive correlation with milder presentation. Mild hemolytic anemia is apparent by 3 months of age. Splenomegaly is usually detected by 6 months of age.

Children with palpable spleen within 6 months of age are at risk of developing subsequent pneumococcal septicemia. Majority of patients experience first episode of vaso-occlusive crisis between 6 months and 6 years.

## Fever and Bacteremia

Fever in a child with sickle cell anemia is a medical emergency, requiring prompt medical evaluation and delivery of antibiotics because of the increased risk of bacterial infection and subsequent high mortality rate. Infants with sickle cell anemia, as early as 6 months of age, develop abnormal immune function due to splenic infarction. By 5 years of age, most children with sickle cell anemia have complete functional asplenia. Regardless of age, all patients with sickle cell anemia are at increased risk of infection and death from bacterial infection, particularly encapsulated organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis*.

The rate of bacteremia in children with SCD, presenting with fever in busy pediatric emergency department is less than 1%. Several clinical strategies have been developed to manage children with sickle cell anemia who present with fever. These vary from hospital admission for IV antimicrobial therapy to administering a third-generation cephalosporin in an emergency department or outpatient setting to patients without established risk factors for occult bacteremia.

## Infections

Fatal *Streptococcus pneumoniae* sepsis occurred in 15–20% of children in the first 5 years of life. These infections were typically fulminant, with death occurring within 24 hours of the onset of fever. Children with SCD have an unusual vulnerability to severe pneumococcal sepsis due to their early loss of splenic reticuloendothelial function (functional hyposplenism) and their lack of circulating antibodies against polysaccharide-encapsulated bacteria.

In early life, the spleen, although often palpably enlarged, loses reticuloendothelial function because of continuous vaso-occlusive infarction. The enlarged spleen gradually becomes small and fibrotic, and it is rarely palpable after 6 years of age. The combination of hyposplenism and lack of antibodies against polysaccharide antigens accounts for the high susceptibility and the historically high frequency and mortality of pneumococcal infections in young children with HbSS.

Patients with SCD also have a predilection for osteomyelitis, perhaps because certain pathogens can survive and escape immunologic clearance in ischemic or infarcted bone and bone marrow. *Salmonella* species cause about half the cases of osteomyelitis in SCD, staphylococci cause most of the rest. It can be difficult to differentiate osteomyelitis from an acute painful episode that results in infarction of cortical bone. Both can cause bony tenderness, effusions, and lucencies on X-ray imaging. Even bone scans and magnetic resonance imaging (MRI) fail to distinguish between the two. Clinical features are more helpful than imaging studies in this situation. The occurrence of fever, a single locus of pain, and a positive blood culture are more consistent with a diagnosis of osteomyelitis than an acute painful episode.

Outpatient management of fever without a source should be considered in children with the lowest risk of bacteremia and after IV ceftriaxone or other cephalosporin is given. In the event that *Salmonella* sp. or *Staphylococcus aureus* bacteremia occurs, strong consideration should be given to an evaluation for osteomyelitis with a bone scan given the increased risk of osteomyelitis in children with sickle cell anemia when compared to the general population.

## Sickle Cell Pain

Dactylitis, referred to as hand-foot syndrome, is often the first manifestation of pain in infants and young children with sickle cell anemia, occurring in 50% of children by their 2nd year of life. Dactylitis often manifests with symmetric or unilateral swelling of the hands and/or feet (**Fig. 2**). Unilateral dactylitis can be confused with osteomyelitis, and careful evaluation to distinguish between the two is important because treatment differs significantly. Dactylitis requires palliation with pain medications, such as hydrocortisone, whereas osteomyelitis requires at least 4–6 weeks of IV antibiotics. Given the recent association between genotype and metabolism of codeine,



**Fig. 2:** Dactylitis.

a subgroup of children may not get pain relief from codeine.

Skeletal pain (bone or bone marrow infarction) with or without fever must be differentiated from osteomyelitis. Both *Salmonella* sp. and *Staphylococcus aureus* cause osteomyelitis in children with sickle cell anemia, which is often in the diaphysis of long bones (in contrast to children without sickle cell anemia where osteomyelitis is in the metaphyseal region of the bone). Differentiating osteonecrosis from a vaso-occlusive crisis and osteomyelitis is often difficult; patients with osteomyelitis often have a longer duration of fever and pain, swelling of the affected area, fewer or only one location of pain and tenderness, higher white blood cell (WBC) counts, and an elevated C-reactive protein. Blood cultures, when positive, are helpful.

MRI findings suggestive of osteomyelitis include localized medullary fluid, sequestrum, and cortical defects. Ultimately, aspiration with or without biopsy and culture will be needed to differentiate the two pathological processes.

## Painful Episodes

The acute painful episode is the hallmark of SCD. It is the most common reason for medical consultation and hospitalization in this population. The pain seems to be caused by acute vaso-occlusion, primarily in bones and bone marrow, with consequent ischemia and inflammation.

Pain can occur anywhere in the body, but it is most commonly osteoarticular and juxtavertebral. The earliest physical manifestation of HbSS is often a characteristic painful episode of dactylitis, an often symmetric swelling of the hands and feet that occurs in about 30% of children in the first 3 years of life. As the child ages, painful episodes instead

involve the long bones, vertebrae, sternum, ribs, lower back, and abdomen.

The treatment of the painful episode is symptomatic and focuses on controlling the severity of the pain. Analgesia must be tailored to the degree of pain and to the patient. Moderate pain without fever or other signs of concomitant illness can usually be managed at home with hydration, analgesics, and rest. However, some pain is so severe that hospitalization for IV hydration and parenteral opioids are necessary. Overhydration is not helpful and may actually precipitate acute chest syndrome (ACS). A combination of non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics, titrated to effect, will usually achieve adequate pain relief.

A useful strategy in patients admitted for inpatient pain management is to initiate patient-controlled analgesia (PCA), consisting of IV opioid medication administered at a continuous (basal) rate with available on-demand (bolus) dosing under the patient's control. Frequent assessments of the number of on-demand doses requested, along with the patient's self-report of the adequacy of pain control and clinical monitoring for adverse effects of opioid therapy, can permit rapid titration to adequate analgesia, at which point the transition to oral long- and short-acting opioids can be initiated.

Patients with SCD-related pain, even severe, typically have no accompanying physical signs, such as edema or erythema, so it is important to trust the patient's report of pain and its intensity and to use this self-report to titrate analgesia. Transfusion does not relieve acute sickle cell pain, and there is currently no therapy to shorten the duration of the painful episode. The pain must be treated until the episode resolves spontaneously, which may take as long as a week. Once the pain begins to resolve, opioid therapy can be weaned relatively quickly.

## Neurologic Complications

Neurologic complications associated with sickle cell anemia are ranging from acute ischemic stroke with focal neurologic deficit to clinically silent abnormalities found on radiologic imaging. A functional definition of overt stroke is the presence of a focal neurologic deficit lasting for >24 hours and/or abnormal neuroimaging of the brain indicating a cerebral infarct on T2-weighted MRI corresponding to the focal neurologic deficit. The complications include headaches that may or may not correlate to degree of anemia, seizures,



cerebral venous thrombosis and reversible posterior leukoencephalopathy syndrome, and also referred to as posterior reversible encephalopathy syndrome (PRES).

## Renal Complications

Renal disease among patients with SCD is a major comorbid condition that can lead to premature death. Seven SCD nephropathies have been identified: (i) gross hematuria, (ii) papillary necrosis, (iii) nephritic syndrome, (iv) renal infarction, (v) hyposthenuria, (vi) pyelonephritis, and (vii) renal medullary carcinoma. As expected, the presentation of these entities is varied but may include hematuria, proteinuria, renal insufficiency, concentrating defects, or hypertension.

## Vaso-occlusive Crisis

The cardinal clinical feature of sickle cell anemia is acute vaso-occlusive pain. No written definition can describe the visual picture of a child with sickle cell anemia experiencing pain. Acute sickle cell pain is characterized as unremitting discomfort that can occur in any part of the body but most often occurs in the chest, abdomen, or extremities.

The exact etiology of pain is unknown, but the pathogenesis is initiated when blood flow is disrupted in the microvasculature by sickled cells, resulting in tissue ischemia. Vaso-occlusive crisis occurs because of blockage of microvascular circulation leading to ischemic tissue injury. There are episodes of painful crisis, which vary in intensity and duration lasting from few days to few weeks.

The precipitating factors include hypoxia, infection, fever, acidosis, dehydration, sleep apnea, and exposure to cold. Emotional or physical stress can be precipitating cause. Sometimes the etiology is idiopathic. Successful treatment of painful episodes requires education of both the caregivers and patients regarding the recognition of symptoms and the optimal management strategy.

## Hand-Foot Syndrome

The age of occurrence could be as early as 4 months. The prevalence is highest at 2 years of age and is rare after 5 years. Ischemic necrosis and death of active bone marrow initiates inflammatory response, and hence increasing intramedullary pressure.

Clinically, there is swelling over the affected small bones of the four extremities, with severe

pain and tenderness. Fever is a common accompanying feature. WBC count is increased up to 15,000/cu mm.

Radiological changes are limited to soft tissue swelling. Cortical thinning and destruction of metatarsals, metacarpals and phalanges follow. Usually complete clinical and radiological recovery occurs within 2–3 weeks. Sometimes damaged epiphysis may cause premature fusion and permanent shortening of small bones. Management consists of hydration and analgesia. Blood transfusion is usually not required.

## Avascular Necrosis of Femoral Head

Avascular necrosis (AVN) occurs at a higher rate among children with sickle cell anemia than in the general population, and is a source of both acute and chronic pain. Most commonly, the femoral head is affected. In AVN, hip and shoulder joints can be affected, but weight-bearing makes femoral head necrosis more likely to cause severe disability. It can occur at any age after infancy, however, the incidence is high in second or third decade. Other sites affected include the humeral head and mandible. Risk factors for AVN include HbSS disease with  $\alpha$ -thalassemia trait, frequent vaso-occlusive episodes, and elevated hematocrit (for patients with sickle cell anemia).

Total collapse and destruction of femoral head can occur after closure of epiphysis. Patient presents with pain in groin and buttock with restriction of movements of hip joint. Radiological changes appear after long time; MRI or radio-nuclide imaging can detect earliest changes associated with pain.

Initial management may include referral to a physical therapist to address strategies to increase strength and decrease weight-bearing daily activities that may exacerbate the pain associated with AVN. Opioids are often used, but usually can be tapered after the acute pain has subsided with AVN. Considerable healing and recovery can occur if AVN occurs before closure of epiphysis of femoral head.

Initial treatment in children and teenagers consists of avoidance of weight-bearing and judicious use of analgesics in first 6 months. Osteotomy with rotation of femoral head to change the weight-bearing are has also been used. In older patients with severe pain but no radiological evidence of collapse, decompression of femoral head results in immediate pain relief. Replacement of hip joint may be done in patients with incapacitating pain interfering daily activities.



## Abdominal Crisis

It occurs predominantly in childhood due to small infarcts of the mesentery and abdominal viscera. There is severe abdominal pain and signs of peritoneal irritation. Persistence of bowel sound differentiates it from acute abdomen requiring surgical exploration. It usually resolves in a period of 4–5 days. The management consists of bowel rest and maintenance of hydration by IV fluids.

## Pulmonary Complications

*Acute chest syndrome* is one of the common causes of hospital admissions in patients of SCD. Acute chest pain, dyspnea, hypoxia, fever, and prostration characterize it. Radiologically, it is characterized by appearance of new pulmonary infiltrates. X-ray changes may take several days to appear. Hematologically, it is characterized by a sudden drop in hemoglobin concentration, increase in leukocyte count and platelet count. The term “acute chest syndrome” is used because a more precise etiology is rarely documented.

*Lung disease* in children with sickle cell anemia is the second most common reason for hospital admission and is associated with significant mortality. ACS refers to a life-threatening pulmonary complication of SCD defined as a new radiodensity on chest radiography plus any two of the following: fever, respiratory distress, hypoxia, cough, or chest pain.

Infection is the most well-known etiology, yet only 30% of ACS episodes will have positive sputum or bronchoalveolar culture, and the most common pathogens are *S. pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydia* spp. The most frequent event preceding ACS is a painful episode requiring systemic opioid treatment. Fat emboli have been implicated as a cause of ACS, arising from infarcted bone marrow, and can be life-threatening if large amounts are released to the lungs.

Pulmonary hypertension has been identified as a major risk factor for death in adults with sickle cell anemia. The natural history of pulmonary hypertension in children with sickle cell anemia is unknown.

The causative factors are thought to be: (i) infection, (ii) in situ vaso-occlusion in lungs due to erythrocyte stasis, (iii) pulmonary infarction due to immobilization from deep vein thrombus or of fat from infarcted marrow, and (iv) analgesic narcotic induced hypoventilation hereby enhancing sickling. In children infectious etiology is common,

whereas on adults in situ vaso-occlusion is more common.

Oxygen should be administered for patients who demonstrate hypoxia. Blood transfusion therapy using either simple or exchange (manual or automated) transfusion is the only method to abort a rapidly progressing ACS episode.

Commonly, blood transfusions are given when at least one of the following clinical features are present: decreasing oxygen saturation, increasing work of breathing, rapid change in respiratory effort either with or without a worsening chest radiograph, a drop in hemoglobin of 2 g/dL below their baseline, or previous history of severe ACS requiring admission to the intensive care unit (ICU).

Treatment usually consists of broad-spectrum antibiotics even in absence of infection for prevention of secondary infection. Severe episodes should be monitored by pulse oximetry, and blood gas analysis. Deterioration of pulmonary functions should be treated as an emergency and can be dramatically reversed by exchange transfusion. Oxygenation and ventilator support should be provided whenever required.

Management includes maintenance of hydration without overhydration, adequate but not excessive analgesia, good airway clearance with incentive spirometry or other measures, bronchodilators if there is any component of reactive airway disease, and antibacterials. An infectious etiology is often not apparent; however, the use of empiric antibiotics active against *Pneumococcus*, *Mycoplasma*, and *Chlamydia* (typically a macrolide and a third-generation cephalosporin) is prudent. It is also important to initiate anti-influenza therapy if there is any clinical suspicion of influenza.

Corticosteroids such as dexamethasone may also be beneficial, but their role has not been demonstrated in controlled clinical trials. Supplemental oxygen can be provided as needed but should be closely monitored, as an increasing oxygen requirement is a sign of worsening disease.

Simple RBC transfusions can be helpful in interrupting disease progression, especially if anemia has worsened from the patient's baseline. Exchange transfusions may be needed for severe cases of ACS requiring significant oxygen supplementation or ventilatory support. Patients with evidence of right heart strain or respiratory distress out of proportion to findings on lung imaging should also undergo evaluation for pulmonary embolism. It is important to perform a thorough

assessment of pulmonary function in patients who have experienced severe or recurrent episodes of ACS, both to assess for chronic lung damage and to identify potentially reversible airway or lung disease.

## Stroke

There are three main clinical presentations of overt cerebrovascular disease in HbSS: (i) cerebral infarction, (ii) cerebral hemorrhage, and (iii) transient ischemic attacks (TIAs). Infarction and hemorrhage cause weakness, paralysis, aphasia, and sometimes seizures and headache. TIAs are episodes of weakness, paralysis, or aphasia that lasts less than 24 hours. TIAs are likely to be overlooked in young children, but they are harbingers of overt stroke. All three presentations can occur at any age, but hemorrhagic stroke is more common in patients older than 20 years.

Stroke is usually preceded by very severe headache. Rapid progressive generalized deterioration may progress to coma. The patient may exhibit decorticate or decerebrate posturing. Associated signs of acute tissue injury due to vaso-occlusive crisis involving lungs, kidney, and liver should be noted.

Other risk factors include anemia, painful episodes, and high white cell count. Hemorrhagic stroke presents with generalized phenomenon such as coma, headache, and convulsions.

MRI and magnetic resonance angiography (MRA) are needed to visualize cerebral infarction and stenosis of intracranial arteries. Computed tomography (CT) scan can be obtained more quickly than MRI, and it may be helpful when cerebral hemorrhage is strongly suspected. MRI and MRA are more sensitive for detecting intracranial hemorrhages and infarctions in the early period.

Acute management includes exchange transfusion, careful hydration, and control of any seizures. An additional 20–30% of patients experience covert or silent cerebral infarctions (SCIs) that are not accompanied by motor signs. Both overt and covert strokes can cause neurocognitive impairment.

These patients need admission in ICU. Ventilator support with facilities for positive end-expiratory pressure (PEEP) or oscillating ventilator devices are necessary. Seizures should be controlled with anticonvulsant drugs. Exchange transfusion to reduce the HbS level to less than 30% should be done. A regular transfusion program designed to keep HbS < 30%, lowers the recurrence rate to 10%. This should be continued for 2–5 years.

## Priapism

Priapism is defined as an unwanted persistent painful erection of the penis and most commonly affects males with sickle cell anemia. The mean age of first episode is 15 years, although priapism has been reported in children as young as 3 years. Priapism occurs in two patterns: prolonged, lasting more than 4 hours, or stuttering, with brief episodes that resolve spontaneously but may occur in clusters and herald a prolonged event. Both types occur from early childhood to adulthood. Most episodes occur between 3 AM and 9 AM in early morning. Priapism in SCD represents a low flow state caused by venous stasis from sickling of RBCs in the corpora cavernosa. Recurrent prolonged episodes of priapism are associated with impotence.

- Recurrent acute priapism manifests with episodic short attacks, which subside spontaneously. Impotency may be a sequela.
- Acute prolonged priapism is characterized by very painful penile erection that does not subside for several hours. Radionuclear scan shows very low blood flow.
- Chronic priapism may follow an acute episode or may arise de novo. The penis is semi-erected, there is no pain. Scan shows good blood flow.

The optimal treatment for acute priapism is unknown. Urology consultation is required to initiate this procedure, with appropriate input from a hematologist.

Treatment includes supportive measures, such as a hot shower, short aerobic exercise, or pain medication, is commonly done by patients at home. A prolonged episode lasting >4 hours should be treated by aspiration of blood from the corpora cavernosa followed by irrigation with dilute epinephrine to produce immediate and sustained detumescence. Transfusion therapy is indicated, if engorgement persists for 24–48 hours. In severe cases, exchange transfusion should be done.

Surgery involving creation of temporary fistula between glans and corpora cavernosa is the treatment of choice if there is no improvement 48 hours after exchange transfusion.

## Sequestration Crisis

Acute splenic sequestration is a life-threatening complication occurring primarily in infants and young children with sickle cell anemia. Sequestration can occur as early as 5 weeks of age but

most often occurs in children between the ages of 6 months and 2 years. The event is characterized by sudden trapping of blood in spleen or less commonly in liver. These patients bleed into their spleen. They present with sudden weakness, significant pallor with profound anemia tachycardia, tachypnea and enormously enlarged spleen filling the abdomen.

Splenic sequestration is associated with rapid spleen enlargement causing left-sided abdominal pain and a decline in hemoglobin of at least 2 g/dL from the patient's baseline. Sequestration may lead to signs of hypovolemia as a result of the trapping of blood in the spleen and profound anemia, with total hemoglobin falling below 3 g/dL, has been reported. Reticulocyte count is markedly elevated and thrombocytopenia is noticed. The condition must be promptly treated within hours of first sign of this disturbance. Hypovolemic shock and death can occur. Subacute episodes are characterized with moderate splenomegaly reduction of hemoglobin level by 2–3 g, and increased reticulocyte count.

Treatment includes early intervention and maintenance of hemodynamic stability using isotonic fluid or blood transfusions. Careful blood transfusions with RBCs are recommended to treat both the sequestration and the resultant anemia. Blood transfusion aborts the RBC sickling in the spleen and allows release of the patient's blood cells that have become sequestered, often raising the hemoglobin above baseline values. 5 mL/kg of RBCs is recommended because the goal is to prevent hypovolemia. Blood transfusion that results in hemoglobin levels above 10 g/dL may put the patient at risk for *hyperviscosity syndrome*, because blood may be released from the spleen after transfusion.

If a child gets two or more episodes, splenectomy is advised. Parents should be educated for regular palpation of spleen enabling them to seek medical treatment in time.

## Aplastic Crisis

RBC lifespan is greatly shortened from the normal of 120 days to 10–20 days in HbSS. Consequently, patients must chronically maintain a marked increase in RBC production by the bone marrow producing a chronic reticulocytosis, to maintain a stable hemoglobin concentration compatible with life. If RBC production is impaired for even a short time, the hemoglobin concentration will fall rapidly. During many viral infections and inflammatory states, erythropoiesis may be

modestly reduced, resulting in relative reticulocytopenia and transiently more severe anemia. Human parvovirus B19, the agent causing fifth disease, has especially profound effects on patients with chronic hemolytic anemia.

Parvovirus destroys early RBC precursors in the bone marrow and causes RBC aplasia for about a week. The consequent erythroidopenia and reticulocytopenia cause a dramatic and potentially life-threatening anemia, with the hemoglobin concentration falling as low as 1–2 g/dL without measurable reticulocytes. This episode of severe anemia is called an aplastic crisis. There may be variable degrees of leukopenia or thrombocytopenia due to the effects of parvovirus. Bilirubin concentration and jaundice are also acutely decreased because there are fewer sickle erythrocytes undergoing hemolysis.

It is characterized by acute anemia, which may lead to readily preventable mortality in young children. The causative organism is parvovirus B19. The parvovirus has direct toxicity to erythroid precursors, colony forming unit.

The clinical features are often interrupted by sickle cell crisis due to suddenly enhanced intravascular sickling. The patient gets pain and ache in the body. Jaundice becomes pronounced. Anemia worsens and spleen enlarges rapidly. The child would be easily fatigued. The patients present with increased fatigue, dyspnea, anemia, and few or no reticulocytes. The condition is always self-limiting with duration of 7–10 days.

Physical growth is retarded. Onset of the puberty is delayed. Clubbing of the fingers is present due to chronic anoxia. Heart size is enlarged. Hemic murmur, i.e., ejection systolic murmur is found on auscultation of the heart. Liver size is enlarged due to sinusoidal dilatation. The spleen becomes palpable at the age of 9 months and may reach up to umbilicus. Then it shrinks due to infarction by the end of the first decade. This is functionally hyposplenic. Flow murmur and venous hum is auscultated. Dehydration may occur. These patients are vulnerable to pneumococcal meningitis and septicemia.

The hemoglobin may drop to 2 g%. Urgent transfusion is required. Daily monitoring of reticulocyte count should be done. The parvovirus offers lifelong immunity.

The acute RBC aplasia is transient and self-limited. Spontaneous recovery begins about 1 week after the onset of reticulocytopenia due to antibody-mediated clearance of the virus. Recovery is heralded by the appearance of nucleated RBCs

in the circulation, followed shortly by a brisk reticulocytosis.

Transfusion of blood is the most important intervention for symptomatic or severe anemia. In contrast to acute splenic sequestration, blood must be transfused relatively slowly in patients with aplastic crisis because their blood volume is typically normal or increased as a physiologic adaptation to a more slowly progressive anemia. Lifelong immunity against parvovirus prevents recurrent episodes.

#### GENERAL FEATURES

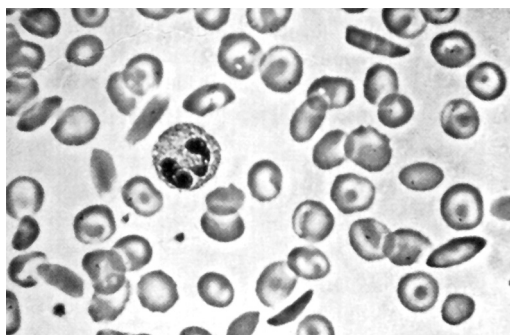
- Acute sickle cell dactylitis
- Hand-foot syndrome
- Priapism
- Cardiomyopathy
- Gallstone formation
- Underweight

### DIAGNOSIS

Beyond the immediate newborn period, the laboratory evaluation of suspected SCD should include a complete blood count, reticulocyte count, and examination of the peripheral blood smear. To confirm a diagnosis of SCD, however, some analysis of hemoglobin types must be performed. Abnormal hemoglobins must be identified using at least two methods because they can be difficult to differentiate.

Because patients with SCD have a chronic hemolytic anemia, they also have unconjugated hyperbilirubinemia and variable elevations of lactate dehydrogenase (LDH) and aspartate transaminase (AST). The bilirubin is a product of heme degradation, and LDH and AST are released from RBCs that undergo hemolysis. After the 1st year of life, the peripheral blood smear shows variable numbers of pathognomonic irreversibly sickled cells, as well as polychromatophilic cells, Howell-Jolly bodies, poikilocytes, and target cells. Howell-Jolly bodies are nuclear remnants, and their presence on the blood smear outside the immediate neonatal period is indicative of hyposplenism.

- *Peripheral smear*—contain variations of sickbed form of RBIs (**Fig. 3**). Target cells are in abundance. Features suggestive of accelerated erythropoiesis such as polychromatophils, basophilic stippling, normoblasts are prominent. Reticulocyte count ranges from 5 to 30%. Heinz bodies, Howell-Jolly bodies are present. WBC count ranges from 8,000 to 20,000/cu mm.
- *Coagulation profile*—platelet count is increased—factor 8, factor 13, fibrinogen,



**Fig. 3:** Sickle cells.  
(For color version see Plate 2)

fibrinolytic activity,  $\beta$ -thromboglobulin are increased factor 12, Prekallikrein are decreased. Alterations in coagulation system are thought to be responsible for occlusive complications of the SCD either directly or in the formation of fibrin strands and platelet aggregation. They may modulate the cell-vessel interaction.

- *Sickling test*—principle is maneuvers used to extract oxygen, cause red cells with HbS to assume sickle shape, whereas cells lacking HbS maintain normal configuration. This can be achieved by sealing a blood drop under cover slip to exclude oxygen, or by adding agent like 2% sodium metabisulfite.
- *Solubility test*—blood containing HbS is added to a buffered solution of a reducing agent like sodium dithionite. Deoxy HbS is precipitated and solution becomes turbid. However, other hemoglobins, such as Hb C-Georgetown, HbI, Hb Bart's, unstable hemoglobins, are also precipitate by this test.

Both above tests are screening test. Diagnosis of a neonatal screening of high-risk population should be done for SCD. Antenatal diagnosis can be done at 8–10 weeks of gestation, with chorionic vials biopsy, or amniocentesis.

#### LABORATORY SALIENT FINDINGS

- Anemia
- Reticulocytosis
- Peripheral blood smear—sickle cells, Heinz bodies, Howell-Jolly bodies
- Sickling test and solubility test

*Definite diagnosis is done by:*  
Electrophoresis of blood lysate on cellulose acetate at alkaline pH 8.6. Certain hemoglobin variants have same electrophoretic mobility as that of HbS



on cellulose acetate electrophoresis. For their differentiation:

- Citrate agar electrophoresis at an acidic pH
- Isoelectric focusing
- Globin chain electrophoresis should be done.

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes rheumatic fever, rheumatoid arthritis, osteomyelitis, and leukemia.

### ESSENTIAL DIAGNOSTIC POINTS

- Genetic mutation leads to abnormal beta-globin chain
- Anemia, elevated reticulocyte count, and musculoskeletal or abdominal pain
- Splenomegaly in early childhood
- High risk of bacterial sepsis
- Hemoglobin electrophoresis: HbS > HbA
- Dactylitis (painful hand or foot swelling)

## TREATMENT

### General Management

Treatment is aimed to prevent serious complication. Administration of a polyvalent pneumococcal vaccine may be beneficial. Prophylactic penicillin is highly effective in preventing serious pneumococcal infections. Oral penicillin can be given starting from 4 months of age. By 5 years of age, this can be discontinued.

Prompt parenteral antibiotics is given for infants and young children with acute onset of high fever.

Preventive care and family education about the potential complications of SCD are important components of SCD management. To this end, the primary care clinician or the hematologist should stress the importance of adherence to penicillin prophylaxis and the standard childhood immunization schedule to prevent early infection. The clinician should also provide anticipatory guidance about surveillance for fever, respiratory distress, pallor, jaundice, splenic enlargement, and neurologic abnormalities, all of which could represent the onset of significant complications of SCD. Early intervention and prompt medical care may be critical in averting life-threatening or severely debilitation morbidities if such symptoms emerge.

There are three main disease-modifying treatments that can reduce the overall severity of SCD or cure it: (i) hydroxyurea, (ii) chronic transfusions, and (iii) hematopoietic stem cell transplantation.

## Hydration

High incidence of hyposthenuria, reduced fluid intake, and increased insensible water loss make them prone for dehydration. Loss of electrolytes may lead to red cell dehydration precipitating sickling process. Fluid requirement is usually increased by 50% of the usual maintenance fluid requirement. Monitoring of electrolytes is necessary.

## Drugs for Severe Pain

Painful episodes or acute crisis is managed with oral acetaminophen alone or with codeine. Severe episodes may require hospitalization and parenteral administration of narcotics. Anti-inflammatory agents especially ketorolac is very useful. Dehydration or acidosis should be rapidly corrected by IV fluids. Transfusion of RBCs can provide relief to disabling chronic pain. For children with stroke, cardiomyopathy and other complication, long-term transfusion regimens are mainstay. Packed RBCs are used for spleen sequestration. Splenectomy is indicated if there are repeated episodes of pain.

Bone marrow transplantation from the normal donor is helpful. Chemotherapy is helpful to stimulate HbF synthesis. The damage includes hydroxyurea and butyrate.

- Injection morphine—0.1–0.15 mg/kg per 3 hourly; oral morphine—0.3–0.6 mg/kg per 3 hourly
- Injection meperidine—0.75–1.5 mg/kg/dose per 3 hourly; oral meperidine—1.5 mg/kg/dose per 3 hourly

## Drugs for Mild Pain

- Codeine—0.5–1 mg/kg/dose every 4 hours orally
- Aspirin—10 mg/kg/dose orally, enhances analgesia if given with narcotic
- Ibuprofen—5–10 mg/kg/dose every 8 hours orally
- Acetaminophen—10 mg/kg/day every 4 hours orally, enhances analgesia with narcotic
- Naproxen—10 mg/kg/day orally
- Indomethacin—1–3 mg/day every 6 hours orally

## Hydroxyurea

Hydroxyurea, a myelosuppressive agent, is the only drug proven effective in reducing the frequency of painful episodes. In a large clinical trial of adults with sickle cell anemia, hydroxyurea was found to decrease the rate of hospitalization for



painful episodes by 50% and the rate of ACS and blood transfusion by almost 50%. Follow-up of the original trial found that adults taking hydroxyurea had shorter hospital stays and required less pain medication during hospitalization. In children with sickle cell anemia, a safety feasibility trial of hydroxyurea demonstrated that hydroxyurea was safe and well tolerated in children >5 years of age. Infants treated with hydroxyurea also experienced fewer episodes of pain, dactylitis, and ACS, and were less-often hospitalized or received a blood transfusion. Despite being a myelosuppressive agent, the infants treated with hydroxyurea did not experience increased rates of bacteremia or serious infection.

The typical starting dose of hydroxyurea is 15–20 mg/kg given once daily, with an incremental dosage increase every 8 weeks of 5 mg/kg, and if no toxicities occur, up to a maximum of 35 mg/kg/dose. The infant hydroxyurea study found young children could safely be started at 20 mg/kg/day without increased toxicity. Achievement of the therapeutic effect of hydroxyurea can require several months, and for this reason, inpatient initiating of hydroxyurea is not optimal.

## Role of Blood Transfusion

Red blood cell transfusions are frequently used in the management of children with sickle cell anemia, both in the treatment of acute complications such as ACS, aplastic crisis, splenic sequestration, and acute stroke, and to prevent surgery-related ACS and first stroke in patients.

Patients with sickle cell disease are at increased risk of developing alloantibodies to less-common red cell surface antigens after receiving even a single transfusion. In addition to standard cross-matching for major blood group antigens (A, B, O, RhD), more extended matching should be performed to identify donor units that are C-, E-, and Kell-antigen negative. Some centers have begun to perform full RBC phenotyping for patients receiving chronic blood transfusions.

Three methods of blood transfusion therapy are used in the management of acute and chronic complications associated with sickle cell anemia: automated erythrocytapheresis, manual exchange transfusion (phlebotomy of a set amount of patient's blood followed by rapid administration of donated packed RBCs), and simple transfusion.

Automated erythrocytapheresis is the preferred method for patients requiring chronic blood transfusion therapy because there is a minimum net iron balance after the procedure, followed by

manual exchange transfusion. Simple transfusion therapy is the least preferable method for regular blood transfusion therapy because this strategy results in the highest net positive iron balance after the procedure. Despite being the preferred method, erythrocytapheresis is less frequently performed because of the requirement of technical expertise, large venous access, multiple units of matched RBCs, and an available apheresis machine.

Blood transfusion in SCD should be used as sparingly as possible, and only for specific indications:

- Severely anemic patients
- Sudden fall of hemoglobin as seen in sequestration crisis
- Acute or suspected cerebrovascular accident
- Multiple organ failure syndrome
- Acute chest syndrome or other acute lung disease where actual oxygenation cannot be maintained near normal even after oxygen therapy and the process is progressive despite of antibiotics given
- Children who have had a cerebrovascular accident, to prevent further similar attacks
- Chronic CCF in conjunction with other treatment.

## Chronic Transfusion

Chronic transfusion programs entail regular, usually monthly, transfusions of packed RBCs (PRBCs) aimed to maintain the percentage HbS in the blood at less than 30%. Transfusion may consist of simple top-off transfusions, phlebotomy transfusions in which a volume of blood is removed before transfusion of nonsickle erythrocytes, or automated exchange transfusion (erythrocytapheresis) in which the patient's erythrocyte mass is continuously removed and replaced with non-sickle erythrocytes. Chronic transfusions are effective at preventing most complications of SCD, but the most common indications are primary and secondary stroke prophylaxis.

Complications of transfusion include iron overload and the need for chelation therapy, alloimmunization, and transfusion-transmitted infections. Iron chelation to prevent toxicity from transfusional iron overload is done.

Preparation for surgery for children with SCD requires a coordinated effort between the hematologist, surgeon, and primary care provider. ACS and pain are the two most common post-operative complications, with ACS being a significant risk factor for postoperative death.

Blood transfusion prior to surgery for children with sickle cell anemia is recommended to raise the hemoglobin level preoperatively to no more than 10 g/dL, although benefit also may be seen at lower hemoglobin values.

## Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell (or bone marrow) transplantation (HSCT) is the only cure for SCD. Widespread use of transplantation is limited by the lack of donor availability and toxicities of the procedure. Transplantation is safest when hematopoietic stem cells are obtained from a human leukocyte antigen (HLA)-matched sibling without SCD, but only 10% of patients actually have a potential donor. The use of alternative donors is an area of ongoing study.

The only cure for sickle cell anemia is transplantation with HLA-matched hematopoietic stem cells from a sibling or unrelated donor. The most common indications for transplant are recurrent ACS and stroke. Sibling-matched stem cell transplantation has a lower risk for graft-versus-host disease than unrelated donors.

## Excessive Iron Stores

The primary toxic effect of blood transfusion therapy relates to excessive iron stores, which can result in organ damage and premature death. Excessive iron stores develop after 100 mL/kg of red cell transfusion, or about 10 transfusions.

The primary treatment of excessive iron stores resulting from RBC transfusion requires iron chelation using medical therapy. The three chelating agents are commercially available and approved for use in transfusional iron overload. *Deferoxamine* is administered subcutaneously 5 of 7 nights/week for 10 hours a night. *Deferasirox* is an effervescent tablet that is dissolved in liquid and taken by mouth daily, and *deferiprone* is available in tablets taken orally a day. The Food and Drug Administration (FDA) approved deferasirox,

the newer oral chelator for use in patient's age  $\geq 2$  years.

## Drugs Augmenting Hemoglobin F Synthesis

Hemoglobin F (HbF) does not copolymerize with HbS, and interferes with bonding of the tactoids. Agents augmenting HbF synthesis thus offer protective effect against gelation (5-azacytidine, hydroxyurea, and butyric acid analogs).

## Antisickling Agents

These can be covalent and noncovalent.

*Covalent agents* act at various sites of globulin chain to decrease deoxy-Hbs gelation or to increase oxygen affinity of hemoglobin or by both mechanisms. They bind to hemoglobin irreversibly. Example is cyanale.

*Noncovalent agents* bind reversibly with hemoglobin. They reduce gelation of sickle hemoglobin by interference with hydrophobic bonds between hemoglobin tetramers. Example is urea.

### LONG-TERM MORBIDITIES

- Chronic lung disease
- Renal failure
- Congestive cardiac failure
- Retinal damage
- Chronic leg ulcer
- Aseptic necrosis of hip and shoulder
- Poor growth

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## PRESENTING COMPLAINTS

An 8-month-old girl was brought with the complaints of:

- Not taking feeds since 2 months
- Not gaining weight since 2 months
- Distension of abdomen since 1 month
- Sweating at the time of feeding since 15 days

## History of Presenting Complaints

An 8-month-old child was brought to the pediatric outpatient department with history of not gaining weight and distension of abdomen since last 2 months. Mother told that there was no significant weight gain in the last 2 months. Mother also revealed the history that her daughter was not taking feeds properly. There was history of

sweating at the time of feeding. She also noted that there was distension of abdomen. The child was shown to the family doctor and she was diagnosed as anemic, and iron preparation was given. But mother concluded all these treatments were in vain.

## Past History of the Patient

She was the second sibling of nonconsanguineous marriage. She was born at term with normal delivery. She cried immediately after the delivery. Birth weight of the baby was 2.9 kg. Child started taking breast milk. The child was breastfed exclusively for 3 months. Later weaning started with cereals as per guidance of the family doctor.

The developmental milestones were normal. Child developed neck control by 3 months. She was sitting with support by 6 months. Now she was sitting independently. She had developed social smile by 2 months.

### CASE AT A GLANCE

#### Basic Findings

Height	: 72 cm (50th centile)
Weight	: 7 kg (10th centile)
Temperature	: 37°C
Pulse rate	: 110 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Failure to thrive
- Abdominal distension
- Sweating

##### Examination

- Depressed nasal bridge
- Prominent frontal bone
- Pallor
- Hepatosplenomegaly

##### Investigation

- Hemoglobin : Decreased
- Red blood cells : Decreased
- Reticulocytes : Increased
- Peripheral blood smear : Microcytic hypochromic anemia, basophil stippling
- X-ray skull : Widening of the diploic space

## EXAMINATION

On examination, child was active, alert and was moderately built and nourished. She was playing with the toys on examination table. There was depressed nasal bridge. Prominent frontal lobe was present. Anterior fontanelle was normal. Anthropometric measurements included the length was 72 cm (50th centile) and weight was 7 kg (10th centile). The head circumference was 39 cm.

The child was afebrile, the pulse rate was 110 per minute, and the respiratory rate was 20 per minute. The blood pressure recorded was 70/50 mm Hg. There was pallor, no icterus, no lymphadenopathy, no edema and no cyanosis.

Per abdomen examination revealed presence of mild distension, liver was palpable about 3 cm below the costal margin. It was nontender and soft in consistency. Spleen was palpable about 2 cm. It was nontender, firm in consistency. Cardiovascular system and respiratory system were normal.

## INVESTIGATION

Hemoglobin	: 5 g/dL
Red blood cell count	: $5.5 \times 10^6/\text{cu mm}$
PCV	: 47%
Reticulocyte count	: 1.5%
MCV	: $78 \mu\text{m}^3$
MCH	: 30 pg
MCHC	: 34%
Serum iron	: 200 $\mu\text{g/dL}$ (Normal range: 22–184 $\mu\text{g/dL}$ )
Serum bilirubin	: 3 mg/dL
Peripheral blood smear	: Showed microcytic hypochromic anemia. Basophilic stippling was present
X-ray of the skull	: Showed widening of the diploic space, absence of the outer table and generalized radial striations

## DISCUSSION

It is a heterogeneous disorder recessively inherited resulting from various mutations of the genes which code for globin chains of Hb, leading to reduced or absent synthesis of globin chains and when beta-chain synthesis is affected it is called as beta-thalassemia.

The thalassemia syndrome is heterogeneous group of hereditary disorders of reduced hemoglobin synthesis. There is diminished or absent normal globin chain production. Normally four alpha globin genes are expressed to make the tetrameric globin protein, which then combines with heme moiety to make the predominant hemoglobin that is found in red cells.

The thalassemias are quantitative disorders of hemoglobin. Thalassemia occurs when there is decreased synthesis of generally structurally normal globin proteins. Like qualitative disorders of hemoglobin, quantitative disorders of hemoglobin can also be subdivided by the particular and globin that is affected, e.g., there can be alpha-thalassemias beta-thalassemias.

## GENETICS AND PATHOPHYSIOLOGY

Mutations that decrease the synthesis of alpha-globins cause beta-thalassemia; mutations that decrease the synthesis of beta-globins cause alpha-thalassemia. In general, alpha-thalassemias are caused by deletions of DNA affecting the

alpha-globin alleles, whereas beta-thalassemias are caused by point mutations affecting the beta-globin alleles. There are also distinct embryonic, fetal, and minor adult analogues of the alpha-globins and beta-globins, all of which are encoded by separate genes.

Depending on the number of genes that are deleted, the production of polypeptide chains is diminished. The result is ineffective erythropoiesis, precipitation of unstable hemoglobin and hemolysis as a result of intramedullary RBC destruction. If the synthesis of X-chain is suppressed, all the three normal hemoglobin are reduced. If the beta chains are suppressed then production of adult hemoglobins is affected. This is the most common form of thalassemia.

Thalassemia refers to a group of genetic disorders of globin chain reduction in which there is an imbalance between the alpha-globin and beta-globin chain production. Beta-thalassemia syndromes result from a decrease in beta-globin chains, which results in a relative excess of alpha-globin chains. Beta-thalassemia refers to the absence of production of the beta-globin.

Beta-thalassemia major refers to the severe beta-thalassemia patient who requires early transfusion therapy and often is homozygous for beta mutation. Beta-thalassemia intermedia is a clinical diagnosis of a patient with a less-severe clinical phenotype that usually does not require transfusion therapy in childhood.

Carriers with a single beta-globin mutation are generally asymptomatic, except for microcytosis and mild anemia. In alpha-thalassemia, there is an absence or reduction in alpha-globin production. Normal individuals have four alpha-globin genes. The primary pathology in the thalassemia syndromes stems from the quantity of globin produced, whereas the primary pathology in sickle cell disease is related to the quality of beta-globin produced.

## PATHOPHYSIOLOGY

Two related features contribute to the sequelae of beta-thalassemia major—inadequate beta-globin gene production leading to decreased levels of normal hemoglobin A (HbA) and unbalanced alpha and beta-globin chain production. In beta-thalassemia major, alpha-globin chains are in excess to nonalpha-globin chains, and alpha-globin tetramers ( $\alpha_4$ ) are formed and appear as red cell inclusions. The free alpha-globin chains and inclusions are very unstable, precipitate in red cell precursors, damage the red cell membrane,

and shorten red cell survival leading to anemia and increased erythroid production.

In the alpha-thalassemia syndromes, two genes with two maternal and two paternal alleles control alpha-globin production, which varies from complete absence (hydrops fetalis) to only slightly reduced (alpha-thalassemia silent carrier). In the alpha-thalassemia syndromes, an excess of beta and gamma-globin chains are produced. These excess chains form Bart hemoglobin ( $\text{Gamma}_4$ ) in fetal life and HbH ( $\text{beta}_4$ ) after birth. These abnormal tetramers are nonfunctional hemoglobins with very high oxygen affinity. They do not transport oxygen and result in extravascular hemolysis. A fetus with the most severe form of alpha-thalassemia (hydrops fetalis) develops in utero anemia and fetal loss because HbF production requires sufficient amounts of alpha-globin. In contrast, infants with beta-thalassemia major become symptomatic only after birth when HbA predominates and insufficient beta-globin production manifests in clinical symptoms.

In homozygous thalassemia major, severe thalassemia genes are inherited from both parents, and production of  $\beta$ -chains is markedly reduced. In heterozygous individuals, a normal  $\beta$ -chain is inherited along with thalassemia  $\beta$ -gene or mild  $\beta$ -thalassemia gene.

Production of beta peptide chains is suppressed. Gamma and delta chains may be enhanced. A part of the latter combines with normally produced  $\alpha$ -chains and form excess of fetal hemoglobin. Most of the alpha chains are destroyed in bone marrow. Hence there is ineffective erythropoiesis. Increased erythropoiesis results in expansion of the medullary cavity of various bones.

It is characterized by an imbalance in the production of  $\alpha$ - and  $\beta$ -globin polypeptide chains of hemoglobin.

- In alpha-thalassemia, alpha-chain synthesis is decreased. In beta-thalassemia, beta-chain synthesis is decreased.
- Excessive alpha-chains precipitate in red cell membrane and damages it. This leads to premature red cell destruction both in the bone marrow and peripheral circulation particularly in reticuloendothelial system of spleen (ineffective erythropoiesis and hemolysis)
- Synthesis of gamma chain persists after fetal life.
- Increased fetal hemoglobin with its high affinity for oxygen leads to tissue hypoxia, which in turn stimulates erythropoietin secretion leading to both medullary and extramedullary

erythropoiesis—expansion of bone marrow space causing a characteristic hemolytic facies with frontoparietal and occipital bossing, malar prominence and malocclusions of teeth, and complications that include distortion of ribs and vertebrae and pathological fracture of the long bones, splenomegaly and its complication hypersplenism, hepatomegaly, gallstones and chronic leg ulcers.

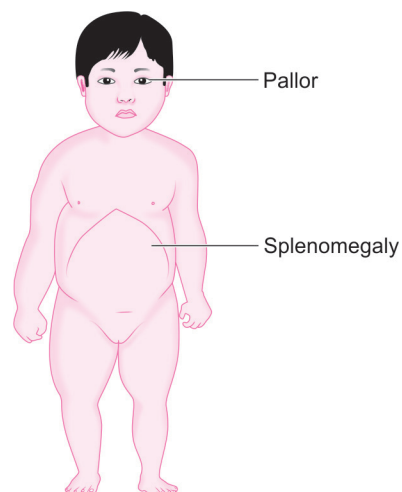
Hypertrophy of the erythropoietic tissue occurs in medullary and extramedullary location. The bones become thin and pathological fracture may occur. Massive expansion of the marrow of skull and face produces characteristic facies.

Extramedullary hematopoiesis produces enlargement of liver and spleen. Breakdown of endogenous or transfused red cells produces the release of iron. This iron is deposited in various organs producing hemosiderosis.

## CLINICAL FEATURES (FIG. 1)

Clinical heterogeneity results from variability in the number of gene deletions particularly in alpha-thalassemia. As a rule, greater the number of deletions, more the symptoms.

The infants are born normally. The child becomes more pale after 4–6 months. Mostly it may be mistaken for iron deficiency anemia. But this will not respond to iron therapy. There will be hepatosplenomegaly. Abdomen will be protuberant. After 1 year mongoloid facies will develop. There will be frontal bossing of the skull. Prominent frontal and parietal eminences, straight forehead, hypertrophy of maxilla, prominent malar eminence, depressed nasal bridge and puffy eyelids. Teeth will be malformed.



**Fig. 1:** Clinical features.



If not treated, children with homozygous beta-thalassemia usually become symptomatic from progressive hemolytic anemia, with profound weakness and cardiac decompensation during the second 6 months of life. Depending on the mutation and degree of fetal hemoglobin production, transfusions in beta-thalassemia major are necessary beginning in the 2nd months to 2nd year of life, but rarely later.

The developing signs of ineffective erythropoiesis such as growth failure, bone deformities secondary to marrow expansion, hepatosplenomegaly are important variables in determining transfusion initiation.

The classic presentation of children with severe disease includes thalassemic facies (maxilla hyperplasia, flat nasal bridge, frontal bossing), pathologic bone fractures, marked hepatosplenomegaly and cachexia and is now primarily seen in countries without access to chronic transfusion therapy.

In nontransfused patients with severe ineffective erythropoiesis, marked splenomegaly can develop with hypersplenism and abdominal symptoms. The features of ineffective erythropoiesis include expanded medullary spaces (with massive expansion of the marrow of the face and skull producing the characteristic thalassemic face), extramedullary hematopoiesis, and higher metabolic needs.

Chronic transfusion therapy dramatically improves the quality of life and reduces the complications of severe thalassemia. Transfusion-induced hemosiderosis becomes the major clinical complication of transfusion-dependent thalassemia. Each milliliter of packed red cells contains 1 mg of iron.

Liver hemosiderosis develops after 1 year of chronic transfusion therapy and is followed by iron deposition in the endocrine system. This leads to a high rate of hypothyroidism, hypogonadotropic gonadism, growth hormone deficiency, hypoparathyroidism and diabetes mellitus.

Physical growth is markedly retarded. These develop intermittent due to infection. The course of illness depends upon severity of the disease. Deaths may occur in few years of life due to severe anemia, cardiac and liver failure. However, with current management they can lead near normal life.

Pallor, hemosiderosis and jaundice combine to produce characteristic greenish brown complexion. Liver and spleen is enlarged. Growth is impaired in older children. Puberty is delayed, because of secondary endocrine abnormalities.

Diabetes mellitus results from pancreatic siderosis and intractable arrhythmias, chronic congestive cardiac failure are caused by myocardial siderosis.

#### GENERAL FEATURES

- Severe progressive anemia
- Hemosiderosis
- Jaundice
- Arrhythmias
- Impaired growth
- Diabetes mellitus

The thalassemias can be described simply by two independent nomenclatures: genetic and clinical. The genetic nomenclature refers to the causative mutation, such as alpha-thalassemia or beta-thalassemia, indicating mutations of the alpha- and beta-globin genes, respectively. The clinical nomenclature divides the thalassemia into the asymptomatic, carrier or trait state (thalassemia minor), severe transfusion-dependent anemia (thalassemia major), and everything in between (thalassemia intermedia).

The clinical features of beta-thalassemia include:

1. *Thalassemia minor*: Minimal or no anemia; microcytosis, elevated RBC count.
2. *Thalassemia intermedia*: Microcytic anemia, growth failure, hepatosplenomegaly, hyperbilirubinemia, thalassemic facies (frontal bossing, mandibular malocclusion, prominent malar eminences), develop between the age of 2 and 5 years.
3. *Thalassemia major (Cooley's anemia)*: Severe anemia, hepatosplenomegaly and growth failure.

#### DIAGNOSIS

The level of the hemoglobin is reduced. The hemoglobin level falls progressively to <6 g/dL unless transfusions are given. The reticulocyte count is commonly <8% and is inappropriately low when compared to the degree of anemia as a result of ineffective erythropoiesis. Fetal hemoglobin level is increased. Total erythrocyte count is low. Reticulocyte count is raised. Hematocrit is reduced, and microcytosis (MCV), hypochromia (MCH), and targeting characterize the red cells.

The peripheral blood smear shows microcytic hypochromic anemia. Anisocytosis and poikilocytosis are present. Fragmented red cells, early, intermediate and late erythroblasts are seen. Nucleated red cells marked anisopoikilocytosis, and a relative reticulocytopenia are typically seen. Marked basophil stippling is seen. Reticulocyte count ranges from 2 to 4%.

The bone marrow is hypercellular with erythroid hyperplasia, with the increased number of stippled erythroblasts and sideroblasts. Myeloid ratio is reversed. Hemosiderin deposits in the marrow is increased.

The unconjugated serum bilirubin level is usually elevated. Bone marrow hyperplasia can be seen on radiographs. Hemoglobin electrophoresis is diagnostic. Fetal hemoglobin is increased in the patient and HbA2 is over 3.4% in both parents.

#### LABORATORY SALIENT FINDINGS

- Reduced hemoglobin.
- Increased fetal hemoglobin.
- Reduced hematocrit.
- MCV, MCH or MCHC are low.
- Hypercellular bone marrow and erythroid hyperplasia.
- Microcytic hypochromic anemia.

The fragility of the cells on exposure to hypotonic saline is decreased. Serum bilirubin level is moderately elevated. It depends upon the rate of hemolytic activity. Serum iron levels are high. Serum ferritin levels are markedly raised.

Earliest bone changes occur in small bones of the hand. Medullary portion is widened and bony cortex is thinned out. There will be coarse trabecular pattern in medulla.

Diploic spaces in the skull are widened. Interrupted porosity gives hair on end appearance on radiography of the skull. The frontal bones appear thickened.

Radiological findings include widening of medulla due to bone marrow hyperplasia, thinning of cortex and trabeculation in the long bones and metacarpals and metatarsals. Skull X-ray shows “hairs-on-end” appearance.

Periodic tests for organ disfunction is necessary which include SGOT, SGPT, serum bilirubin, serum calcium, endocrinal studies, etc.

#### DIFFERENTIAL DIAGNOSIS

- Iron-deficiency anemia
- Sickle cell anemia
- Hookworm infestation
- Methemoglobinemia

#### ESSENTIAL DIAGNOSTIC POINTS

- Quantitative reduction in globin synthesis
- Expansion of fascial bones—extramedullary hematopoiesis
- Microcytic hypochromic anemia
- No response to iron therapy
- Marked hepatosplenomegaly

#### TREATMENT

Thalassemia trait (thalassemia minor) requires no treatment. The lifelong hypochromic, microcytic anemia neither requires nor responds to iron supplementation. Establishing a diagnosis of thalassemia trait will prevent repeated unnecessary diagnostic tests and inappropriate treatment with iron. It is important, however, to counsel individuals with either alpha- or beta-thalassemia trait regarding the risk of having offspring with a significant hemoglobinopathy. The risk of clinically significant alpha-thalassemia disease is dependent on both the exact genotype of the individual and that of the partner. Individuals with  $\beta$ -thalassemia trait can also have affected offspring with significant variability in disease severity depending on the severity of each parent  $\beta$ -thalassemia mutation. Additionally, individuals with  $\beta$ -thalassemia trait can have offspring with other hemoglobinopathies, such as sickle  $\beta$ -thalassemia or Hb E- $\beta$ -thalassemia, depending on the partner's carrier status.

Patients with thalassemia intermedia, by definition, do not require regular or chronic transfusions of RBCs. However, intermittent simple transfusions may be needed in the event of illness or complications. For example, infection with parvovirus (the cause of erythema infectiosum or fifth disease) causes an aplastic crisis that may require transfusion. Other causes of worsening anemia include infection and drug-mediated hemolysis, splenectomy may benefit patients who develop significant hypersplenism with severe anemia. Cholecystectomy may be necessary for symptomatic cholelithiasis caused by pigmented gallstones or cholecystitis. Sometimes chelation therapy for iron overload is needed for older individuals, especially if they have received multiple transfusions.

By definition, patients with thalassemia major are transfusion dependent. Historically, transfusions were given sparingly and did not effectively prevent many of the consequences of severe anemia and marrow expansion. More vigorous transfusion programs designed to maintain a minimum hemoglobin concentration of 10 g/dL or higher (hypertransfusion) were instituted.

Generally, modern chronic transfusion regimens are given to alleviate the severe anemia and to suppress and greatly diminish ineffective erythropoiesis. When started early in life and continued thereafter, chronic transfusions can prevent bony and dental abnormalities, decrease extramedullary hematopoiesis, normalize growth and development, and prolong and improve quality of life.

Transfusions are usually given monthly and sometimes more frequently to maintain a nadir hemoglobin concentration in the 9.5–10 g/dL range. The risks of blood transfusions include alloimmunization, hemolytic and nonhemolytic transfusion reactions, transfusion-transmitted infections, and iron overload.

## Transfusion Therapy

Before initiating chronic transfusions, the diagnosis of transfusion dependent beta-thalassemia should be confirmed by both clinical and laboratory parameters. beta-thalassemia major is a clinical diagnosis that requires the integration of laboratory findings and the clinical course.

The long-term observation of the clinical characteristics, such as growth, bony changes, and hemoglobin, are necessary to determine chronic transfusion therapy.

Transfusion therapy in thalassemia has two goals:

1. To prevent anemia
2. To suppress endogenous erythropoiesis to avoid ineffective erythropoiesis.

Blood transfusion is mandatory for all children with thalassemia major and for those children with thalassemia intermedia who cannot maintain Hb above 7 g% or those who show evidence of growth retardation, severe bony changes. Regular blood transfusions are presently the mainstay of treatment of thalassemia major.

Cross-matched triple saline washed packed cells are transfused to avoid transfusion reactions as saline washing minimizes reactions due to depletion of leukocytes and plasma proteins. If cold centrifuge that is required if not available, simple packed cells may be given. Other means of decreasing sensitization includes use of leukocyte filter and frozen cells.

Transfusion regimen may be (1) low transfusion regimen when Hb maintained around 7–10 g%, (2) hypertransfusion: Hb. Level 10–12 g% and supertransfusion when Hb maintained is above 12–14 g%.

The popular transfusion regimen of today is a hypertransfusion regime which aims at maintaining mean hemoglobin levels at 12.5 g/dL and pretransfusion level not less than 10 g%. Such a regimen permits normal growth and physical activities, suppresses erythropoiesis, thus preventing skeletal changes and gastrointestinal iron absorption and also inhibits extramedullary hemopoiesis, thereby preventing splenomegaly and hypersplenism. With this regime, requirement of blood is high only at the start of therapy, and

does not produce an iron overload more than the low transfusion regime.

## Guidelines for Transfusion Therapy

Patients at risk for transfusion therapy should have an extended red cell phenotype and/or genotype. Patients should receive red cells depleted of leukocytes and matched for, at least, D, C, c, E, e, and Kell antigens.

Transfusions should generally be given at intervals of 3–4 weeks, with the goal being to maintain a pretransfusion hemoglobin level of 9.5–10.5 g/dL. Ongoing monitoring for transfusion-associated transmitted infections (hepatitis A, hepatitis B, hepatitis C, HIV), alloimmunization, annual blood transfusion requirements, and transfusion reactions is essential.

## Amount and Frequency of Transfusion

It is desirable that patients receive not more than 10 cc packed cells/kg/day, which raises Hb level by about 3.5 g/dL. In most of patients, transfusion of about 10 cc of packed RBC/kg every 3rd week is adequate to maintain pretransfusion baseline Hb level desired 10–11 g/dL.

Rate of transfusion should be 5–7 mL/kg body weight/h to avoid sudden increase in blood volume. In patients with cardiac insufficiency transfusions may have to be given every 2nd week and sometimes every week and prolong the duration of transfusion by decreasing the rate to 1–3 mL/kg/h not more than 5 mL/kg/h.

Transfusions should preferably be given on an outpatient basis, at intervals of 2–4 weeks. Blood to be transfused should be crossmatched using Coombs sera to minimize reactions. Blood should be taken from a voluntary donor and should be screened for hepatitis B antigen, syphilis, malaria and HIV and also for hepatitis C virus (HCV) antibodies.

The patients should be assessed annually for mean hemoglobin levels maintained, overall blood requirement, physical growth and development, evidence of hypersplenism, antibody development and iron overload. On an average the annual blood requirement is 180–200 mL/kg. However, if the requirement exceeds this level, hypersplenism or development of antired cell antibodies have to be considered.

## Neocyte Transfusion

This concept of transfusing thalassemic children with young red cells (Neocytes). In conventionally used unit of blood, red cells have a survival of 60 days. The mean age of a neocytes being 12 days,

they survive in the recipient for 90 days, thus reducing the amount of blood required and prolonging the interval between two transfusions. Neocyte, exchange transfusion though have been tried, are found to be impracticable.

## Iron Overload Monitoring

Excessive iron stores from transfusion cause many of the complications of beta-thalassemia major. Accurate assessment of excessive iron stores is essential to optimal therapy. Serial serum ferritin levels are a useful screening technique in assessing iron balance trends, but results may not accurately predict quantitative iron stores. Under treatment or over treatment of presumed excessive iron stores can occur in managing a patient based on serum ferritin alone.

Iron loading is monitored by serum tests of iron stores (ferritin) liver biopsy, and iron quantitation by. MRI can be used to estimate iron deposition in the liver, pancreas, and heart. After about 200 mL/kg of RBCs have been transfused; chelation is usually necessary.

## Iron Overload and Chelation Therapy

Two factors contribute to iron overload in thalassemic child:

1. Enhanced gastrointestinal absorption of iron
2. Transfusional siderosis normal body iron content is 3–5 g, whereas in a thalassemic child it could be around 0.75 g/kg.

Transfusional iron overload leads to deposition of iron in the heart leading to cardiomyopathy and irregularity of heartbeats, in the pancreas, in the islet of Langerhans leading to diabetes, in the liver and spleen leading to hepatosplenomegaly, hepatic fibrosis and cirrhosis of liver, in the pituitary glands leading to growth retardation, delayed puberty character, in the thyroid and parathyroid gland leading to subclinical or clinical organ dysfunction, and in the skin leading to bronze or black discoloration of skin.

Increased susceptibility to bacterial infection especially *Yersinia* with iron overload, because the relatively high serum iron levels may favor bacterial growth, or because of blockage of the mononuclear phagocyte system by the excessive red cell destruction.

Iron accumulation in the myocardium can lead to death, either by involving the conducting tissues or by causing intractable cardiac failure due to cardiomyopathy.

Iron-chelation therapy should start as soon as the patient becomes significantly iron overloaded. In general, this occurs after 1 year of transfusion

therapy and correlates with the serum ferritin >1,000 ng/mL and/or a liver iron concentration of >2,500 µg/g dry weight.

There are three available iron chelators (deferroxamine, deferasirox, and deferiprone); each varies in its route of administration, pharmacokinetics, adverse events, and efficacy. Many patients require combination chelation therapy at various points in their illness. The overall goal is to prevent hemosiderosis-induced tissue injury and avoid chelation toxicity. This requires close monitoring of the patients. In general, chelation toxicity increases as iron stores decrease.

Deferoxamine is the most studied iron chelator. It has an excellent safety and efficacy profile. Deferoxamine (DFO) is a hydroxylamine compound produced by *Streptomyces pilosus*. A single gram of DFO is able to bind 85 mg of iron. Deferoxamine should be started before the age of 3–5 years.

It requires subcutaneous, or intravenous, administration because of a half-life of less than 30 minutes, necessitating administration of at least 8 hours daily, 5–7 days/week. Deferoxamine is initially started at 20 mg/kg and can be increased to 60 mg/kg, in heavily iron-overloaded patients given on daily basis for a minimum of 5–6 times per week, it is given subcutaneously over 6–8 hours using an infusion pump. The daily dose of deferral is about 30–70 mg/kg and should be tailored according to the need of the patient. In general, the goal is to keep the serum ferritin level below 1000 ng/mL.

The major problem with deferoxamine is non-compliance because of the route of administration. Adverse side effects include ototoxicity, retinal changes, and bone dysplasia with truncal shortening.

The oral iron chelator deferasirox is commercially available in of patients on Desferal, 70% have switched to deferasirox because it is orally available. Deferasirox has a half-life of more than 16 hours and requires once-a-day administration of a dispersal tablet in water. Initial dose is 20 mg/kg with gradual escalation to 30 mg/kg. The most common side effects are gastrointestinal symptoms.

Deferiprone (Ferriprox), an oral iron chelator has a half-life of approximately 3 hours and requires 25 mg/kg three times a day. Deferiprone, a small molecule, effectively enters cardiac tissue and may be more effective than other chelators in reducing cardiac hemosiderosis. The most serious side effect of deferiprone is transient agranulocytosis, which occurs in 1% of patients.

The use of deferiprone enquires weekly white blood cell counts.

It mobilizes iron from transferring, ferritin, and hemosiderin. Dose: 50–100 mg/kg/body weight. Physical examination particularly of the joints and complete blood count including platelet count must be done regularly when child is on Deferiprone (L1) therapy.

With recent advances in chelation therapy especially with the availability of oral chelating drugs like Deferiprone (L1) compliance has remarkably improved. The cost of therapy has reduced considerably and hence even in the developing countries many children are able to use the drug.

Deferoxamine, in combination with deferiprone, is routinely used in patients with increased cardiac iron. Combination therapy of deferoxamine and deferasirox may also be efficacious in similar patients.

## Role of Vitamin C

Ascorbic acid deficiency increases insoluble iron hemosiderin. Vitamin C helps in conversion of hemosiderin into ferritin from which iron can be chelated.

- High doses of vitamin C can lead to increased free radical reaction and lipid peroxidation resulting in tissue damage and rapid cardiac decompensation and even death.
- Addition of vitamin C 100 mg daily prior to DF therapy increases iron excretion.
- Sixty percent of desferrioxamine chelated iron is excreted in urine, and 40% in stool.

## Hydroxyurea

Hydroxyurea, a DNA antimetabolite, increases stress erythropoiesis, which results in increased HbF production. It has been most successfully used in sickle cell disease and in some patients with beta-thalassemia intermedia.

Hydroxyurea therapy in thalassemia intermedia may have other benefits including decreasing the vascular disease associated with thalassemia intermedia. The initial starting dose for thalassemia intermedia is 10 mg/kg and because these patients are more sensitive to toxicity than sickle cell disease, higher doses are used with great caution.

## Hematopoietic Stem Cell Transplantation

Stem cell (or bone marrow) transplantation is the only cure for thalassemia. More than 1000 transplants have been done worldwide. Transplantation

is safest when hematopoietic stem cells are obtained from a human leukocyte antigen (HLA)-identical sibling (without thalassemia), but only 25% of siblings will be HLA identical. The use of alternative donors is an area of ongoing study.

For well-chelated children without liver disease, event-free survival at 5 years after transplantation is 85–95%, depending on the report. Results are considerably worse in adults and in patients who are poorly compliant with chelation and have hepatic disease. The relatively high immediate mortality associated with transplantation stands in contrast to the many years of reasonably normal life that can be obtained with appropriate transfusion and chelation therapies, which makes the decision to accept transplantation difficult for many families.

Most success has been in children younger than 15 years of age without excessive stores and hepatomegaly who undergo sibling HLA-matched allogeneic transplantation. All children who have an HLA-matched sibling should be offered the option of bone marrow transplantation. Alternative transplantation regimens for patients without donors are experimental and have variable success.

## Splenectomy

With the advent of hyper and super transfusion therapy, splenomegaly and hypersplenism have become a rarity and hence splenectomy is usually not needed in these patients.

Splenectomy may be required in thalassemia patients who develop hypersplenism. These patients have a falling steady state hemoglobin and/or a rising transfusion requirement. Overall, splenectomy is less frequently used as a therapeutic option.

If the child has already developed splenomegaly and signs of hypersplenism and is above 5 years of age, splenectomy is indicated. The indications for splenectomy are an increase in the yearly requirement of packed cells more than double the basal requirement, i.e., packed cell 200 cc/kg/year or more. Decrease in WBC and platelet count is late manifestation of hypersplenism.

There is an increased recognition of serious adverse effects of splenectomy beyond infection risk. In thalassemia intermedia, splenectomized patients have a marked increased risk of venous thrombosis, pulmonary hypertension, leg ulcers, and silent cerebral infarction compared to non-splenectomized patients.

There is an increased risk of bacterial sepsis following splenectomy, especially in young children.



Hence, antibacterial prophylaxis with pneumococcal vaccination is necessary. There is also evidence that splenectomy increases the risk of thrombosis and, perhaps, pulmonary hypertension.

All children needing splenectomy should receive pneumococcal vaccine, *H. influenzae* vaccine, and meningococcal vaccine 4–6 weeks prior to surgery or earlier. In endemic areas prophylactic antimalarial treatment may be given to prevent malaria.

Prophylactic penicillin therapy must be continued life-long after splenectomy. Episodes of infection should be treated promptly and newer broad spectrum antibiotics may be empirically started to prevent septicemia and other complications. If necessary these children should be hospitalized. Blood culture and antibiotic sensitivity must be performed to guide treatment.

## Bone Marrow Transplantation

A ray of hope for permanent cure and better future for children with genetic disorders has brightened with the rapid advancement in the techniques and the success of bone marrow transplantation.

The principles of bone marrow transplantation in thalassemia are: (a) to destroy and prevent regeneration of defective stem cells, (b) sufficient immune suppression for good engraftment of normal marrow, (c) to infuse stem cell with normal gene for  $\beta$ -chain globin, (d) to prevent graft versus host disease (GVHD) with high dose therapy of Busulphan, Cyclophosphamide, total body irradiation and other modalities.

The three most important adverse prognostic factors for survival and event-free survival are the

1. Presence of hepatomegaly (liver more than 2 cm below costal margin)
2. Portal fibrosis
3. Iron overload

Bone marrow transplantation is most successful in patients who are young, properly transfused, well-chelated and in good clinical shape without hepatomegaly.

## Gene Manipulations

It has been tried to increase the production of HbF and to prevent the precipitation of unpaired Hb chains. Augmenting the production of  $\gamma$ -chain reduces imbalance of globin chain and increases synthesis of HbF and thus lessening the severity of the disease. Those drugs being tried are 5-Azacytidine, Hydroxyurea, Butyrate derivatives, ICL 670, hydroxybenzyl ethylenediamine (HBED) and pyridoxal isonicotinoyl hydrazone (PIH).

Hydroxyurea has been found to increase HbF level. It is not found to be useful in thalassemia major. However, it has been found to help in prolongation of interval in blood transfusion and in alleviating symptoms of children with sickle cell anemia and thalassemia intermedia.

## Butyrates

These are found naturally increased in diabetic mothers. Their babies at birth have 100% HbF.

This drug is given IV infusion slowly over 6–8 hours in dose of 200–400 mg/kg/day has been shown to increase in HbF by 8–12%, rise in Hb by 2–3 g%. Problem with this drug is the tedious intravenous route. Oral analogue Na Butyrate is useful in some patients to sustain the response after intravenous therapy. The side effects are few and include nausea, vomiting, electrolyte disturbances, occasional seizure.

## ICL-670

During the last couple of years new synthetic oral chelator ICL-670A has given a ray of hope. It belongs to tridentate triazole group and is undergoing phase III trial.

Iron is chelated both from reticuloendothelial cells as well as parenchymal organs. It also has the ability to prevent myocardial cell iron uptake and remove iron directly from myocardial cells. Iron excretion is predominantly fecal. It excretes iron from both reticuloendothelial cells as well as parenchymal cells of various organs and chelated iron excreted by liver through the bile. Only side effects reported include mild abdominal pain, gastrointestinal discomfort, constipation, skin rash. No changes in auditory, visual (ocular) or cardiac functions were observed. It also has the ability to prevent myocardial cell iron uptake, remove the iron directly from myocardial cells and exchange the iron with DFO. Coadministration of ICL 670 with injection DFO has synergic effect and helps in reducing dose of both the drugs thus improving the compliance and cost of the treatment as is done with oral chelation therapy with deferiprone.

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# Acute Poststreptococcal Glomerulonephritis

## PRESENTING COMPLAINTS

A 6-year-old boy was brought with the complaints of:

- Skin lesions since 2 weeks
- Puffiness of face since 1 week
- Passing high colored urine since 2 days

## History of Presenting Complaints

A 6-year-old boy was brought to pediatric outpatient department with history of puffiness of face around the eyes since 1 week. Mother noticed swelling around eyes. This used to be more in morning. Swelling used to reduce as day passes on. There was no history of swelling of lower limbs of the body.

This was associated with history of passing high colored urine. There was no history of burning

sensation while passing the urine. There was no history of increased frequency of micturition.

## Past History of the Patient

He was the elder sibling of nonconsanguineous marriage. He was born at full-term by normal delivery. He cried immediately after delivery. His birth weight was 3 kg. He was exclusively on breast milk for 3 months. Later weaning was started and he was on family food by 15 months. His developmental milestones were normal. He was immunized completely. His performance at school was good.

There was development of oozing skin lesions treated with the course of antibiotics and local antiseptic ointment. There was no history of fever, convulsions, suggestive of oliguria, sore throat and breathlessness.

## CASE AT A GLANCE

### Basic Findings

Height	: 124 cm (95th centile)
Weight	: 20 kg (70th centile)
Temperature	: 37°C
Pulse rate	: 86 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 100/80 mm Hg

### Positive Findings

#### History

- Puffiness of face
- High colored urine
- 2-week-old skin lesions

#### Examination

- Periorbital edema
- Healed skin lesions
- Raised blood pressure

#### Investigation

- ESR: Raised
- BUN: Raised
- Creatinine: Raised
- ASLO: Significant
- Urine: Albumin, RBCs, granular casts, 10–12 pus cells observed
- X-ray chest: Showed pulmonary venous congestion and cardiomegaly

## EXAMINATION

On examination, the body was moderately built and moderately nourished. He was alert. There were healed pyogenic skin lesions. Anthropometric measurements included, the height was 124 cm (95th centile), and the weight was 20 kg (70th centile).

Child was afebrile, the pulse rate was 86 per minute regular. Respiratory rate was 20 per minute. Blood pressure recorded was 100/80 mm Hg in right upper limb. Pallor was present. Periorbital edema was present. There was no clubbing and no lymphadenopathy. All the systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 8 g/dL
TLC	: 8,700 cells/cu mm
Platelet count	: 2,00,000 cells/cu mm
ESR	: 32 mm in 1st hour
BUN	: 40 mg/dL
Serum creatinine	: 4 mg/dL
HbSag	: Negative

ASLO	: 200 Todd units
Complement level	: C3 decreased
Serum potassium	: 4 mEq/L
Serum sodium	: 130 mEq/L
Peripheral blood smear	: Normocytic hypochromic anemia
Serum bilirubin	: 1.3 mg/dL
Pus for culture and sensitivity	: No growth
Urine examination	: Albumin present. Granular casts, plenty of RBCs and 10–12 pus cells were present
X-ray chest	: Pulmonary venous congestion and cardiomegaly

## DISCUSSION

A school going child developed sudden onset of puffiness of the face. This was more around the face. This was also associated with history of high colored urine probably hematuria. There was significant history of treatment for pyodermic lesions about 2 weeks back.

On examination, there was periorbital edema and moderately raised blood pressure. All these findings make a diagnosis of acute poststreptococcal glomerulonephritis. This is supported by raised blood urea level and serum creatinine level.

Group A beta-hemolytic streptococcal infections are common in school-age children and is more common in boys and can lead to the postinfectious complication of acute glomerulonephritis (GN). Acute poststreptococcal glomerulonephritis (APSGN) a classic example of the acute nephritic syndrome characterized the sudden onset of gross hematuria, edema, hypertension, and insufficiency.

Acute glomerulonephritis is characterized by a relatively abrupt onset of variable degrees of hematuria, edema, hypertension, oliguria along with diminished glomerular filtration rate (GFR), salt and fluid retention and circulatory congestion.

## ETIOLOGY

Acute glomerulonephritis may follow infection with a variety of microorganisms, when it is called “postinfectious”. Acute glomerulonephritis occurring after  $\beta$ -hemolytic streptococcal infection is the commonest type in children, accounting for approximately 80% cases. However, many other

bacterial, viral, and parasitic pathogens may also induce acute postinfectious glomerulonephritis (PIGN). Identifying a specific causative pathogen often is difficult because the infection usually precedes the nephritis by a few weeks. Other agents responsible for nephritis are influenza A, coxsackie, ECHO virus, Epstein-Barr virus, *Staphylococcus* and *Pneumococcus*. Acute glomerulonephritis may occur as part of a systemic disease and acute nephritic features may be observed in acute interstitial nephritis.

Poststreptococcal glomerulonephritis commonly follows streptococcal pharyngitis during cold-weather months and streptococcal skin infections or pyoderma during warm-weather months. APSGN has been shown to be nephritogenic following pharyngitis (strain 3, 4, 12, 18, 25, and 49) or impetigo (strains 2, 49, 55, 57, and 60). It is extremely rare for APSGN and acute rheumatic fever (associated with M strains 1, 3, and 12) to occur simultaneously in the same patient. Although epidemics of nephritis have been described in association with throat (serotypes M1, M4, M25, and some strains of M12) and (serotype M49) infections, this disease is most commonly sporadic.

## PATHOLOGY

Glomeruli appear enlarged and relatively bloodless and show diffuse mesangial cell proliferation, with an increase in mesangial matrix. Neutrophil infiltration is striking in early stages. The capillary basement membrane and the arterioles do not show significant abnormality. Epithelial cell proliferation and crescents are uncommon. In a very small proportion of cases, however, extensive crescentic changes are present, which is associated with a rapidly progressive course and a poor prognosis.

Polymorphonuclear leukocyte infiltration is common in glomeruli the early stage of the disease. Crescents and interstitial inflammation may be seen in severe cases, but these changes are not specific for poststreptococcal GN. The glomerular abnormalities are very characteristic. Proliferative and exudative changes are uniformly distributed. Glomeruli are enlarged and the lobular pattern is accentuated. There is proliferation of both endothelial and mesangial cells with obliteration of capillary lumen giving the glomeruli a “bloodless” appearance.

Immunofluorescence examination shows granular deposits of immune complexes immunoglobulin G (IgG) and C3 along the capillary walls

and in the mesangium. C1q and C4 deposits may also be seen. Electron microscopy shows electron dense subepithelial deposits or ‘humps’. These are more striking early and tend to disappear after 6 weeks. IgG has been demonstrated in these deposits. Immunofluorescence microscopy reveals a pattern of “lumpy-bumpy” deposits of immunoglobulin and complement on the glomerular basement membrane and in the mesangium. On electron microscopy, electron-dense deposits, or humps: are observed on the epithelial side of the glomerular basement membrane.

The histological abnormalities resolve rapidly and within 6–8 weeks there is considerable decrease in exudative changes. Mild mesangial hypercellularity may persist for 1–2 years but eventually disappears. Capillary loops are narrowed. Glomeruli appear enlarged and ischemic changes are seen. There will be proliferation of mesangial cells. There will be infiltration of neutrophils in glomeruli.

## **PATHOGENESIS**

The precise nature of the antigen-antibody complex that causes nephritis remains unclear. The latency period between the acute infection and the onset of nephritis represents the time required to generate sufficient IgG antistreptococcal antibodies to trigger immune complex formation. Morphologic studies and a depression in the serum complement (C3) level provide strong evidence that APSGN is mediated by immune complexes. Circulating immune complex formation with streptococcal antigens and subsequent glomerular deposition is thought less likely be a pathogenic mechanism. Group A streptococci possess M proteins, and nephritogenic strains related to the M protein serotype.

Although several streptococcal antigens have been identified in the glomerular immune deposits, 2 proteins are of particular interest, based on currently available evidence. First is the cationic cysteine proteinase exotoxin B that colocalizes with complement and IgG within glomerular subepithelial immune deposits. The presence of circulating anti-SpeB antibodies is strong evidence of a recent nephritogenic streptococcal infection. Second is the nephritis—associated plasmin receptor, a protein that does not co-localize with glomerular immune deposits but is associated with increased intraglomerular plasmin activity and is thought to facilitate immune complex formation and inflammation.

Additional antigens are of interest and suggest that a group of streptococcal proteins may be involved in the initiation and progression of glomerular injury. It is currently thought that the target streptococcal antigen is initially trapped within glomeruli, with subsequent immune complex formation occurring *in situ* in the kidney. Once glomerular immune deposits are formed, the alternative and lectin complement pathways are activated, followed by neutrophil infiltration and glomerular damage. APSGN is an “exudative” GN characterized by the presence of many intra-glomerular neutrophils. Pyuria and even white cell casts may be observed in the urinary sediment.

### **Postinfectious**

- Streptococci, staphylococci, *Treponema pallidum*, *Salmonella typhi*, leptospirosis.
- *Plasmodium malariae*, toxoplasma, filarial
- Hepatitis B and C, cytomegalovirus, parvovirus, Epstein-Barr virus
- Associated with severe infections; infection of shunts, prostheses, bacterial endocarditis

### **Systemic vasculitis**

- Henoch-Schönlein purpura, systemic lupus erythematosus
- Microscopic polyarteritis, Wegener’s granulomatosis

### **Others**

- Membranoproliferative glomerulonephritis
- IgA nephropathy
- Hereditary nephropathy
- Acute interstitial nephritis

## **GLOMERULONEPHRITIS WITH HYPOCOMPLEMENTEMIA**

- Poststreptococcal
- Subacute bacterial endocarditis
- Shunt nephritis
- Systemic lupus erythematosus
- *Membranoproliferative*
- Other postinfectious causes

## **CLINICAL FEATURES (FIG. 1)**

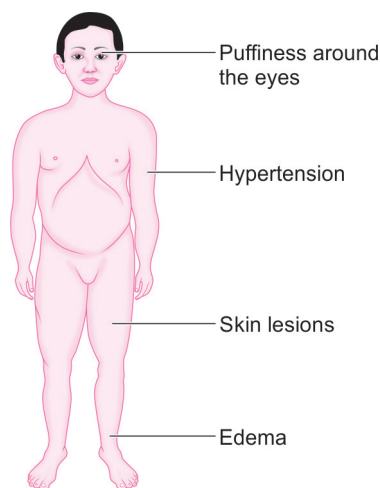
Onset of the disease is sudden. It usually affects children between the ages of 5 and 12 years and is rare below the age of 3 years. A male preponderance is reported. Patients usually are afebrile with a latency period of 1–2 weeks after having pharyngitis and 3–6 weeks after having a skin infection.

There will be puffiness of face with periorbital swelling. Edema is usually the result of salt and water retentions. Some degree of oliguria is usually associated, but anuria is infrequent and if persistent suggests rapidly progressive glomerulonephritis.

If the fluid intake has been unrestricted, the edema may increase to involve the hands and legs.

Gross hematuria (30–50%) will be associated. Urine is typically reddish brown or smoky or cola colored. Hematuria is defined as the presence of more than five red blood cells per high power field on at least two performed urine analysis. Glomerulonephritis is the most important cause of asymptomatic hematuria. Almost all the patients have microscopic hematuria.

In some cases, pharyngitis may be mild and have gone unnoticed. Active or healed lesions of impetigo (**Fig. 2**) may be present when acute glomerulonephritis develops. During an epidemic of streptococcal throat infection, many sub-clinical cases occur who have only microscopic hematuria.



**Fig. 1:** Clinical features.



**Fig. 2:** Impetigo.  
(For color version see Plate 2)

The severity of kidney involvement varies from asymptomatic—microscopic hematuria with normal renal function to gross hematuria with acute renal failure. Depending on the severity of renal involvement, patients can develop various degrees of edema, hypertension, and oliguria. Patients are at risk for developing encephalopathy and/or heart failure secondary to hypertension or hypervolemia. Hypertensive encephalopathy must be considered in patients with blurred vision, severe headaches, altered mental status, or new seizures. Respiratory distress, orthopnea, and cough may be symptoms of pulmonary edema and heart failure. Peripheral edema typically results from salt and water retention and is common; nephrotic syndrome develops in a minority (<5%) of childhood cases. Nonspecific symptoms such as malaise, lethargy, abdominal pain, or flank pain are common.

The acute phase generally resolves within 6–8 weeks. Although urinary protein excretion and hypertension usually normalize by 4–6 weeks after onset, persistent microscopic hematuria can persist for 1–2 years after the initial presentation.

Mild hypertension is usually present. The nonspecific symptoms such as malaise, lethargy, abdominal pain and fever are common. The severity of the renal involvement varies from asymptomatic microscopic hematuria with normal renal function to acute renal failure.

In most cases, there is a history of sore throat or pyoderma. The latent period is 7–14 days in the former and 2–4 weeks in the latter.

The severity of PSGN is variable and mild cases may just have microscopic hematuria with slight proteinuria. Those at the other end of the spectrum may have oligoanuria and severe hypertension.

#### ESSENTIAL DIAGNOSTIC POINTS

- Edema
- Proteinuria—1+
- Transient hypertension
- Oliguria
- *Urinalysis:* Dysmorphic RBCs, red cell casts

The urine often has a unique color or tea color. Rapidly progressive GN can occur, but only rarely. Although many patients have significant proteinuria and a slightly depressed serum albumin level (at least in part due to intravascular volume expansion), fewer than 5% of symptomatic patients develop frank NS. Severe complications, including pulmonary hemorrhage and cerebrovascular accidents, have been reported and can require kidney biopsy to distinguish APSGN from systemic vasculitis or Goodpasture syndrome.



## Atypical Presentations

The child may present with one or more of the complications of AGN. A history of sore throat and gross hematuria may be absent and the edema mild. Occasionally urinalysis may not show significant abnormality. A correct diagnosis and prompt management are crucial.

### *Acute Pulmonary Edema*

Expansion of extracellular volume may lead to congestive heart failure and pulmonary edema. There is dyspnea and restlessness. The blood pressure is high but in later stages when heart failure and shock supervene, there may be hypotension. A chest X-ray film typically shows mild cardiomegaly and features of pulmonary edema. Often the condition is wrongly diagnosed as bronchopneumonia or myocarditis.

### *Hypertensive Encephalopathy*

Children with AGN may develop hypertensive encephalopathy at comparatively lower levels of blood pressure. Drowsiness and convulsions may be the presenting features, and may resemble encephalitis. Measurement of blood pressure and urinalysis is diagnostic.

Hypertension is common (60–80%) but usually is mild to moderate; rarely, hypertensive encephalopathy and posterior reversible encephalopathy syndrome (PRES) can develop, even without a significant elevation in the serum creatinine concentration. Echocardiographic evidence of left ventricular dysfunction is a common finding in children hospitalized with APSGN.

### *Acute Renal Failure*

In occasional cases, oligoanuria and azotemia are the chief features and gross hematuria and edema may be absent.

### *Nephrotic Syndrome*

A mixed picture of AGN and nephritic syndrome may be present. The child has gross hematuria, hypertension, generalized edema and heavy proteinuria. In such cases the glomerular lesions are invariably severe and extensive crescent formation may be present.

## COMPLICATIONS

Complications include those occurring as a consequence of hypertension such as hypertensive encephalopathy and congestive cardiac failure.

Other complications include hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, seizures, and uremia.

Features of delayed resolution:

- Oliguria, hypertension and/or azotemia persisting for past 2 weeks
- Gross hematuria persisting for 3–4 weeks
- Low C3 levels beyond 6–8 weeks
- Persistent hematuria or proteinuria beyond 6–12 months

### GENERAL FEATURES

- Rapid onset
- Hematuria
- Convulsions
- Sore throat

## DIAGNOSIS

The serum C3 level usually is below 50% of normal levels in patients with APSGN. 10% of APSGN patients have normal C3 level at the time of assessment. In patients with other forms of acute PIGN, this percentage is even higher. The serum C3 level typically returns to normal within 8–12 weeks after APSGN. Urinalysis generally shows hematuria, proteinuria, and cellular casts (both red and white cells); rarely, patients may have a normal urinalysis.

Urinalysis demonstrates red blood cells, often in association with red blood cell casts, proteinuria, and polymorphonuclear leukocytes. A mild normochromic anemia may be present from hemodilution and low-grade hemolysis.

Confirmation of the diagnosis requires clear evidence of a prior streptococcal infection. A positive throat culture report might support the diagnosis or might represent the carrier state. A rising antibody titer to streptococcal antigen(s) confirms a recent streptococcal infection.

A fresh, uncentrifuged urine specimen should be examined for casts as these disintegrate on standing and centrifugation. Hyaline and granular casts also may be seen.

The antistreptolysin O titer is commonly elevated after a pharyngeal infection but rarely increases after streptococcal skin infections. Evidence of preceding streptococcal infection is indicated by a rise in antistreptolysin O (ASLO) titer, which is elevated in 60–80% cases. Early antibiotic treatment may attenuate this response. The rise in ASLO titer begins 1–3 weeks after the streptococcal infection, reaches a peak in 3–5 weeks and then falls to insignificant levels in 6 months.

The best single antibody titer to document cutaneous streptococcal infection is the anti-deoxyribonuclease (DNase B) B level. Serologic evidence for streptococcal infections is more sensitive than the history of recent infections and far more sensitive than positive bacterial cultures obtained at the time of onset of acute nephritis.

Gross hematuria is present in a majority of moderate to severe cases. Proteinuria is usually mild; occasionally it may be in the nephrotic range. Microscopic examination shows dysmorphic red cells, red cell casts and neutrophils. In initial stages urine may contain a large number of neutrophils, which is often mistakenly regarded to indicate urinary tract infection.

The blood urea and serum creatinine levels are elevated. In patients with acute renal failure there may be hyponatremia, hyperkalemia and acidosis.

Chest X-ray is indicated in those with signs of heart failure or respiratory distress, or physical examination findings of a heart gallop, decreased breath sounds, rales, or hypoxemia. A chest X-ray film may show cardiomegaly and pulmonary congestion. Anemia and hypoalbuminemia are secondary to renal sodium and water retention with consequent hemodilution.

Renal function studies show a decrease in GFR and renal blood flow, increased distal tubular reabsorption of sodium and water leading to hypervolemia and expansion of extracellular volume. The levels of plasma rennin and aldosterone are decreased. These abnormalities are exactly opposite to those observed in minimal change nephritic syndrome with edema.

#### SALIENT LABORATORY FINDINGS

- *Urinalysis:* Dimorphic RBCs, red cell casts
- *BUN, creatinine:* Raised
- *Serum C3 and C4:* Decreased
- *Streptococcal serology:* ASLO-raised
- *Serum albumin:* Decreased
- Throat culture, skin culture if lesions present
- ANA, anti-DNA antibodies

Magnetic resonance imaging of the brain is indicated in patients with severe neurologic symptoms and can demonstrate posterior reversible encephalopathy syndrome in the parieto-occipital areas on T2-weighted image.

The serum C3 level is significantly reduced in >90% of patients in the acute phase, and returns to normal 8–12 weeks after onset. Serum C5 levels are mildly reduced but those of C4 are normal. Persistent hypocomplementemia is rare in PSGN and suggests an alternative condition such as

membranoproliferative GN, lupus nephritis or GN related to endocarditis or occult abscesses. The degree of C3 depression is not related to the severity of the disease.

Renal biopsy should be considered only in the presence of acute renal failure, nephrotic syndrome, absence of evidence of streptococcal infection, or normal complement levels. In addition, renal biopsy is considered when hematuria and proteinuria, diminished renal function, and/or a low C3 level persist more than 2 months after onset.

Renal biopsy is not required in typical cases of PSGN, except when the serum complement remains depressed or if renal function is severely impaired making the diagnosis questionable. The following table summarizes the situations where a biopsy is indicated. The biopsy is done to assess prognosis or detect the presence of other underlying glomerular diseases such as systemic vasculitis, lupus erythematosus or membranoproliferative GN.

#### INDICATIONS FOR RENAL BIOPSY IN ACUTE GLOMERULONEPHRITIS

- *Systemic features:* Fever, rash, joint pain, heart disease
- Absence of serologic evidence of streptococcal infection; normal level of C3
- Mixed picture of AGN and nephritic syndrome
- Severe anemia, very high levels of blood urea or anuria requiring dialysis
- Delayed resolution:
  - Oliguria, hypertension and/or azotemia persisting past 2 weeks
  - Gross hematuria persisting past 3–4 weeks
  - Low C3 levels beyond 6–8 weeks
  - Persistent hematuria or proteinuria beyond 6–12 months

Immunofluorescence microscopy reveals lumpy bumpy deposits of immunoglobulin and complement in the glomerular basement membrane and mesangium. Peripheral blood smear shows normocytic hypochromic type of anemia. This is because of hemodilution.

#### DIFFERENTIAL DIAGNOSIS

- Nephrotic syndrome
- Hemolytic uremic syndrome
- Urinary tract infection
- Anaphylactoid purpura
- Angioneurotic edema
- Insect bite

## TREATMENT

Treatment of acute glomerulonephritis includes strict bed rest, management of hypertension and congestive cardiac failure. During the acute phase, patients may need to be hospitalized for observation and treatment of hypertension, edema, oliguria, elevated serum creatinine, or electrolyte abnormalities. Intake of sodium, potassium and protein should be restricted. Urine output should be correctly measured. Fluid intake should be restricted to an amount equal to insensible losses and 24-hour urine output.

APSGN is an acute disease that resolves without specific medical therapy. Close monitoring and supportive care are essential to manage the acute nephritis syndrome until the glomerular injury spontaneously resolves. If not previously administered, antibiotics should be given to prevent the spread of the nephritogenic strain of *Streptococcus* to other individuals. Penicillin may be administered for 7 days if active pyoderma or residual pharyngitis is present. Antibiotic therapy has no influence on the course of the disease but may prevent spread of streptococcal infection from patients with positive cultures.

Hypertension usually is not severe and can be managed with short-acting calcium channel blockers. Moderate to severe hypertension with or without encephalopathy usually responds to treatment with nifedipine and furosemide. Beta-adrenergic blockers such as atenolol and angiotensin converting enzyme inhibitors such as enalapril are also useful in lowering blood pressure.

Circulatory congestion and edema can be treated with restriction of salt and water and judicious use of diuretics. In patients having acute pulmonary edema and shock, appropriate supportive measures should be promptly instituted. Dopamine or dobutamine should be infused and ventilatory support may be needed. Furosemide should be given intravenously in a dose of 4–6 mg/kg.

If oliguria is present and the level of blood urea is elevated, dietary protein should be appropriately restricted.

In patients with more severe AKI, hyperkalemia, hyperphosphatemia, and acidosis are likely to occur and will require medical management. Corticosteroids and cytotoxic agents have no substantiated therapeutic role, although there

is limited anecdotal evidence of benefit for patients with rapidly progressive GN associated with crescents on biopsy. This is such a rare presentation that performing prospective clinical trials to evaluate the benefit of such therapies is impossible.

## COURSE AND PROGNOSIS

Spontaneous improvement should begin within 1 week, with the gross hematuria, oliguria, azotemia, and hypertension generally resolving within 4 weeks; low C3 within 2 months, proteinuria by 6 months; and gross hematuria rapidly clears but microscopic hematuria may be detected for 6–12 months or longer. APSGN in children has been considered a completely reversible disease, which is still generally true. In the exceptional patient with crescentic disease, prolonged oliguria, and massive proteinuria, recovery may not be complete. Proteinuria subsides earlier but orthostatic or intermittent proteinuria may be observed. Such urinary abnormalities are of no significance. Occasionally mild to moderate hypertension may persist for a few weeks.

The long-term prognosis of poststreptococcal glomerulonephritis in children is excellent. Even patients with severe disease completely recover; the only exception is the presence of extensive glomerular crescentic lesions. Since immunity to streptococcal M-protein is type specific and long lasting and nephritogenic serotypes are limited in number, recurrent episodes of PSGN are rare. Penicillin prophylaxis is not recommended.

Children with acute glomerulonephritis without evidence of a preceding streptococcal infection should be closely followed for several years with periodic urine examinations and measurements of blood pressure. Renal biopsy may be considered if mild to moderate proteinuria persists or if there is a decline in renal function.

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# Hemolytic–Uremic Syndrome

## PRESENTING COMPLAINTS

A 5-year-old girl was brought with the complaints of:

- Cough and cold since 3 days
- Loose motions since 3 days
- Abdominal pain since 1 day
- Headache since 1 day
- Nausea since 1 day
- Abnormal movement of limb since 1 hour

## History of Presenting Complaints

A 5-year-old girl was brought to the casualty with history of sudden onset of nausea, abdominal pain and headache. Abdominal pain was present in upper abdomen. The pain was not related to food intake. There was no radiation of pain. The child was complaining of headache. Headache was nonspecific. She had been treated for cough

and cold a week back. The medicine used was paracetamol. The girl had loose motion about 3 days back. She was passing loose motion about 6–7 times a day. Loose motion was foul smelling and was associated with blood stain. The condition of the child was worsening despite of parenteral ampicillin. Girl developed convulsions involving both the upper and lower limbs. The convulsions were of generalized type.

## Past History of the Patient

She was the second sibling of nonconsanguineous marriage. She was born at term by normal delivery. She cried immediately after the delivery. There was no significant postnatal event. She was completely immunized. There was no delay in developmental milestones. Her performance at school was good. There was past history of similar attack.

## EXAMINATION

The girl was moderately built and moderately nourished. There were signs of moderate dehydration. She was in distress and looking sick. Anthropometric measurements included, her height was 108 cm (50th centile), and her weight was 17 kg (60th centile).

Girl was febrile, the pulse rate was 120 per minute, and the respiratory rate was 30 per minute. The blood pressure recorded was 70/50 mm Hg. Pallor was present. There was no lymphadenopathy, no icterus and no cyanosis.

Per abdomen examination revealed presence of mild distension. Tenderness was present all over the abdomen. Hepatomegaly was present about 3 cm below the costal margin in the midclavicular region. It is firm in consistency and nontender. Bowel sounds were sluggish. Respiratory system revealed presence of crepitations at the base of right lung.

## INVESTIGATIONS

Hemoglobin : 5.4 g/dL  
TLC : 12,300 cells/cu mm

### CASE AT A GLANCE

#### Basic Findings

Height	: 108 (50th centile)
Weight	: 17 kg (60th centile)
Temperature	: 37°C
Pulse rate	: 120 per minute
Respiratory rate	: 30 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Cough and cold
- Abdominal pain
- Headache
- Loose motions
- Convulsions

##### Examination

- Pale toxic look
- Mild distended abdomen
- Abdominal tenderness
- Hepatomegaly

##### Investigation

- Hb: 5.4 g/dL
- Bilirubin: Increased
- Hyperkalemia
- Blood urea: Increased

PCV	: 30%
Platelet count	: 2,00,000 cells/cu mm
Blood urea	: 42 mg/dL
Serum creatinine	: 1 mg/dL
K	: 6.2 mEq/L
Na	: 100 mEq/L
Peripheral blood smear	: Showed burr cells ( <b>Fig. 55.1</b> )
X-ray chest	: Moderate cardiomegaly, bilateral increased hilar and pulmonary shadow
Ultrasound abdomen	: Mild hepatomegaly

## DISCUSSION

Hemolytic–uremic syndrome (HUS) is the most common cause of acute renal failure in young children. It has common features to systemic disease as well as thrombotic thrombocytopenic purpura and cutaneous signs.

It is characterized by the triad of microangiopathic–hemolytic anemia, thrombocytopenia and acute renal insufficiency. The possibility of a genetic form of the disease should be considered in any child with an atypical presentation.

Two broad subgroups of hemolytic–uremic syndrome are recognized. The first is most commonly seen in infants and young children. It is associated with diarrheal prodrome. It has also been called as typical hemolytic–uremic syndrome. The HUS is the most common glomerular disease to cause severe acute kidney injury (AKI) in a previously healthy young child. Most children with HUS (90%) have an antecedent diarrheal illness caused by a strain of *E. coli* that produces a Shiga-like toxin. This group of patients had been formerly classified as having diarrhea-associated HUS (D+HUS), and this disorder is now known as Shiga toxin-producing *E. coli*-associated (STEC+) HUS.

It more frequently follows an episode of gastroenteritis caused by enterohemorrhagic strain of *E. coli*. It has also been associated with other bacteria such as *Shigella*, *Salmonella*, *Compylobacter*, *Streptococcus pneumoniae*. The viruses responsible for this are coxsackie, influenza and Epstein-Barr viruses.

Several serotypes of *E. coli* can produce the toxin. Disease commonly is transmitted by undercooked meat or unpasteurized (raw) milk. HUS develops during acute infection with this organism, typically manifesting as pneumonia with empyema. A thrombotic microangiopathy, similar to HUS or TTP, also can occur in patients with untreated HIV infection. Second form is not

associated with antecedent hemolytic–uremic syndrome. It usually follows a bacterial or viral infection. It may result from hypertensive encephalopathy and convulsions. Fluid retention occurs secondary to fluid overload because of oliguria and anuria leading to cardiac failure.

It has been associated with systemic lupus erythematosus (SLE), malignant hypertension and pre-eclampsia. The picture of HUS may be mimicked by sepsis, when complicated by consumption coagulopathy especially in young infants. Such cases should be distinguished from HUS. HUS may resemble idiopathic thrombocytopenic purpura (ITP). Whereas thrombotic micro-angiopathy and the resulting hemolytic anemia and thrombocytopenia are common to both of these disorders, their typical profiles are very different.

The features of HUS occasionally may be seen in association with a wide variety of conditions such as bacterial and viral infections, malignancies, collagen diseases, renal transplantation and malignant hypertension, but these are uncommon in children.

Hemolytic–uremic syndrome is occasionally seen following invasive *Streptococcus pneumoniae* infection, in which there is damage to endothelium from streptococcal neuraminidase. That leads to exposure of crypted Thomsen–Friedenreich antigen and absorption of natural circulating antibodies.

Genetic forms of HUS (atypical, nondiarrheal) compose the second major category of the disease. A major feature characteristic of genetic forms of HUS is the absence of a preceding diarrhea prodrome. Genetic forms of HUS can be indolent and unremitting once they become manifest, or they can have a relapsing pattern precipitated by an infectious illness.

## PATHOLOGY

The basic lesion of HUS is termed thrombotic microangiopathy (TMA). Glomerular TMA is very characteristic of HUS and similar lesions are only seen in allograft glomerulopathy and in some forms of chronic rejection. Early lesions are best demonstrated on electron microscopy. The endothelial cells are swollen with increase in intracytoplasmic organelles.

There is peripheral extension of mesangial cell cytoplasm and matrix into capillary wall with narrowing of lumen. Mesangial cells are hypertrophied with increase in rough endoplasmic reticulum and lipid droplets. Finely granular fibrillar material similar to that seen in subendothelial space is present in the mesangium.

Intralobular and arcuate arteries show a mixture of fibrous endarteritis and fibrinoid



necrosis. Interlobar arteries are not involved. The glomeruli are superficial, cortex look ischemic with splitting of capillary wall, widening of subendothelial space and wrinkling of glomerular basement membrane.

Early glomerular changes include thickening of the capillary walls caused by swelling of endothelial cells and accumulation of fibrillar material between endothelial cells and the underlying basement membrane, causing narrowing of the capillary lumens. Platelet-fibrin thrombi are often seen in glomerular capillaries.

## **PATHOGENESIS OF HEMOLYTIC–UREMIC SYNDROME**

Microvascular injury with endothelial cell damage is characteristic of all forms of HUS. Normally, the vascular endothelial lining presents a non-reactive surface to circulating blood cells. Thus, intravascular activation of platelets is prevented. This property is related to the negative charge on the endothelial cell surface, which repels negatively charged platelets and red cells, and also to their synthesis of platelet and coagulation-inhibiting factors (such as prostacyclin, plasminogen activator and heparin sulfate).

In the diarrhea-associated form of HUS, enteropathic organisms produce either Shiga toxin or the highly homologous Shiga-like verotoxin both of which directly cause endothelial cell damage. Shiga toxin can directly activate platelets to promote their aggregation. In pneumococcal-associated HUS, neuraminidase cleaves sialic acid on membranes of endothelial cells, red cells, and platelets to reveal the underlying cryptic Thomsen-Friedenreich (T) antigen endogenous immunoglobulin M (IgM) recognizes the T-antigen and triggers the microvascular angiopathy.

Following severe dysentery Shiga toxin enters the circulation and leads to endothelial injury in the microvasculature. Neutrophils may have a role in endothelial injury and oxidant damage may be important. There is localized coagulation and deposition of platelet thrombi and fibrin in glomeruli. Involvement of other organs, e.g., pancreas and brain may occur.

The initial changes of glomeruli include thickening of the capillary walls and narrowing of capillary lumina and widening of mesangium. There will be subendothelial and mesangial deposition of granular and amorphous material. Fibrin thrombi can be found in glomerular capillaries and arterioles, and may lead to cortical necrosis. There will be partial and total sclerosis of the glomeruli. Ischemia will result as a result of vascular involvement. Concentric intimal

proliferation of the arteries and arterioles lead to vascular occlusion.

In each form of HUS, capillary and arteriolar endothelial injury in the kidney leads to localized thrombosis, particularly in glomeruli causing a direct decrease in glomerular filtration. Progressive platelet aggregation in the areas of microvascular injury results in consumptive thrombocytopenia. Microangiopathic-hemolytic anemia results from mechanical damage to red blood cells (RBCs) as they pass through the damaged and thrombotic microvasculature.

A perturbation in the coagulant-anticoagulant status, following cytotoxin-mediated endothelial cell injury, may lead to coagulation in capillaries and other inflammatory events. Platelets are highly reactive cells, which can be activated by a variety of stimuli such as contact with damaged endothelium, immune complexes, endotoxin, fibrin, platelet activating factor and other vaso-active agents.

Release of von Willebrand factor antigen from the endothelial cells by a cytopathic effect might explain the abnormalities of this factor in the plasma of HUS patients and may be related to platelet agglutination and thrombocytopenia.

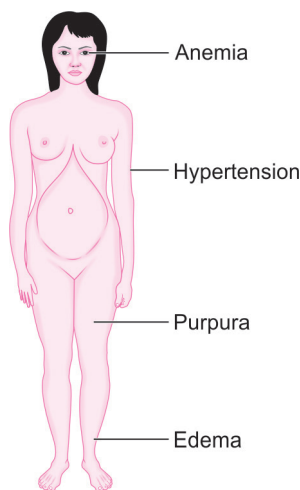
Abnormalities of coagulation and increased blood levels of fibrin degradation products, suggesting DIC may be present in dysentery associated HUS. Localized coagulation evidenced by the presence of fibrin thrombi and platelets in glomerular capillaries is a constant feature.

## **CLINICAL FEATURES (FIG. 1)**

The syndrome is most common in children under the age of 4 years. The onset is preceded by gastroenteritis and less commonly by upper respiratory tract infection. This is followed in about 5–10 days by sudden onset of pallor, irritability, weakness, lethargy and oliguria. This is seen commonly in summer months and may occur in small epidemics. Encephalopathy and more serious extrarenal manifestation can occur. It is uncommon. But hemorrhagic colitis is common.

Hypertension is usually present. Uncommon features include gross hematuria, petechiae and purpura, jaundice and convulsions. Renal involvement is usually severe. With prolonged oliguria and anuria, complication of ARF may present HUS with no diarrhea mostly seen in older children. Many have heavy proteinuria and gross hematuria. Severe hypertension is usually present.

Hemolytic-uremic syndrome can occur in adolescents and adults. In HUS caused by toxigenic *E. coli*, onset occurs a few days after onset of gastroenteritis with fever, vomiting, abdominal pain,



**Fig. 1:** Clinical features.

and diarrhea. The prodromal intestinal symptoms may be severe and require hospitalization, but they can also be relatively mild and considered trivial. The diarrhea is often bloody but not necessarily so. Following the prodromal illness, the sudden onset of pallor, irritability, weakness, and lethargy heralds the onset of HUS.

In patients with HUS following shigellosis, the dysentery is usually severe and persistent and may continue well beyond the development of HUS. In those not related to shigellosis, there is a prodrome of diarrhea, which is mild or severe, and often bloody, and may subside by the time HUS develops. Patients presenting late may show more severe neurological involvement with convulsions and occasionally focal abnormalities. In those with prolonged oliguria or anuria (which correlate with the severity of renal injury) complications of ARF may be present.

Oliguria can be present in early stages but may be masked by ongoing diarrhea, because the prodromal enteritis often overlaps the onset of HUS, particularly with ingestion of large doses of toxins. The patients with pneumococci-associated HUS usually are ill with pneumonia, empyema, and bacteremia when they develop HUS. Onset can be insidious in patients with the genetic forms of HUS, with HUS triggered by a variety of illnesses, including mild, nonspecific gastroenteritis or respiratory tract infections.

The majority of patients with HUS have some central nervous system involvement. Most have mild manifestations, with significant irritability; lethargy, or nonspecific encephalopathic features. Severe CNS involvement occurs in 20% of cases. Seizures and significant encephalopathy are the most common manifestations in those with severe

CNS involvement, resulting from focal ischemia secondary to microvascular CNS thrombosis. Small infarctions in the basal ganglion and cerebral cortex have also been reported, but large strokes and intracranial hemorrhage are rare. Hypertension may produce an encephalopathy and seizures.

Intestinal complications can be protean and include severe inflammatory colitis, ischemic enteritis, bowel perforation, intussusception, and pancreatitis. Patients can develop but petechiae, significant or severe bleeding is rare despite very low platelet counts. Besides intestinal complications (pseudomembranous colitis, perforation and intussusception) that are more common in postdysenteric HUS, involvement of the liver, heart, endocrine and exocrine pancreas and muscles has also rarely been observed. However, most patients who recover do not appear to have residual functional impairment of organs other than the kidney.

#### ESSENTIAL DIAGNOSTIC POINTS

- Microangiopathic–microcytic anemia
- Thrombocytopenia
- Renal insufficiency
- Purpuric rashes
- Diarrhea
- Disseminated intravascular coagulation (DIC)
- Oliguria

#### DIAGNOSIS

The diagnosis is made by the combination of microangiopathic–hemolytic anemia with schistocytes, thrombocytopenia, and some degree of kidney involvement. The anemia can be mild at presentation, but rapidly progresses. Thrombocytopenia is an invariable finding in the acute phase, with platelet counts usually 20,000–100,000/cu mm. Partial thromboplastin and prothrombin times are usually normal.

The diagnosis of the syndrome is supported by findings of microangiopathic–hemolytic anemia, thrombocytopenia and acute renal failure. The peripheral blood smear shows helmet cells, burr cells and fragmented RBCs. Plasma hemoglobin levels are elevated and plasma haptoglobin levels are diminished. The reticulocytes are moderately elevated. White cell count may be elevated, and thrombocytopenia is seen.

The Coombs test is negative, with the exception of pneumococci-induced HUS, where the Coombs test is usually positive. Leukocytosis is often present and significant. Urinalysis typically shows microscopic hematuria and low-grade proteinuria. The renal insufficiency can vary from

mild elevations in serum blood urea nitrogen and creatinine to acute, anuric kidney failure.

**Hemolytic anemia:** Peripheral blood smear characteristically shows broken and deformed RBC. Fragmentation of red cells results from mechanical damage as these cells traverse the abnormal microvasculature through a meshwork of fibrin strands. Increased oxidant damage to RBC membrane may also play a role. Bacterial neuraminidase and phospholipase C can injure endothelial cells, RBC and platelets.

**Thrombocytopenia:** Platelet counts are almost invariably decreased and return to normal in 2–3 weeks. There is enhances platelet consumption; their destruction is chiefly related to contact with damaged vascular endothelium the products of platelet injury cause chemotaxis of neutrophils. Serum levels of serotonin and platelet factor IV are increased.

**Leukocytosis:** Neutrophilic leukocytosis is a very common finding in HUS, especially in the post-dysenteric form. Activated neutrophils release lysosomal enzymes and reactive oxygen radicals that can cause or aggravate endothelial cell damage.

**Coagulation:** Normal levels of fibrinogen and normal fibrinogen turnover in HUS suggest absence of DIC. Raised levels of FDP indicate activation of the fibrinolytic system. Endothelial injury leads to release of large von Willebrand factor polymers that cause platelet aggregation and increased formation of platelet thrombi. Normal levels of fibrinogen rules out DIC. Raised level of FDP indicates activation of fibrinolytic system. Serum concentration of potassium may be low. Urinalysis shows red cells and occasional casts.

**Biochemistry:** Biochemical changes indicative of renal dysfunction are present. Serum concentration of potassium may be low initially in some cases, possible as a result of gastrointestinal losses during the diarrheal prodrome. Urinalysis shows red cells and occasional casts.

**Renal biopsy:** This shows endothelial cells are swollen and separated from the basement membrane with accumulation of foamy material in the subendothelial space. The capillary lumen is narrowed by swollen endothelial cells, blood cells and fibrin thrombi. Arterioles may show similar changes. Patchy or extensive renal cortical necrosis may be present.

In patients with STEC-HUS, establishing etiology requires either stool culture or PCR for STEC or ELISA for Shiga toxin. Serum complement C3 levels are low in some patients with atypical

HUS and abnormalities of the complement system. Detailed analysis of components of the alternative complement pathway and its regulators is recommended in all patients with atypical HUS.

#### LABORATORY SALIENT FINDINGS

- Hemolytic anemia
- Thrombocytopenia
- Leukocytosis
- Negative Coombs test
- Abnormal renal biochemical parameters

#### GENERAL FEATURES

- Hematuria
- Altered sensorium
- Oliguria

### DIFFERENTIAL DIAGNOSIS

- Disseminated intravascular coagulation (DIC)
- Acute glomerulonephritis
- Trauma
- Anaphylactoid purpura

### COMPLICATIONS

Complications include anemia, acidosis, hyperkalemia, fluid overload, congestive cardiac failure, hypertension and uremia. Central nervous system manifestation includes irritability seizures and coma. Colitis and diabetes mellitus are common.

### TREATMENT

The primary approach that has substantially improved acute outcome in HUS is early recognition of the disease, monitoring for potential complications, and meticulous supportive care. Supportive care includes careful management of fluid and electrolytes, including prompt correction of volume deficit, control of hypertension, and early institution of dialysis if the patient becomes significantly oliguric or anuric, particularly with hyperkalemia.

Early intravenous volume expansion before the onset of oligoanuria may be nephroprotective in diarrhea-associated HUS, red cell transfusions are usually required as hemolysis can be brisk and recurrent until the active phase of the disease has resolved. Packed RBCs must be infused slowly or during dialysis, with careful monitoring of the patient's blood pressure. Platelet transfusions should be avoided unless the patients are actively bleeding or the transfusions are needed in preparation for an invasive procedure.

In pneumococci-associated HUS, it is critical that any administered red cells be washed before

transfusion to remove residual plasma, because endogenous IgM directed against the revealed T-antigen can play a role in accelerating the pathogenesis of the disease.

There is no evidence that any therapy directed at arresting the disease process of the most common, diarrhea-associated form of HUS provides benefit. Attempts have been made using anticoagulants, antiplatelet agents, fibrinolytic therapy, plasma therapy, immune globulin, and antibiotics. Prompt treatment of causative pneumococcal infection is important. In adults who were treated with azithromycin demonstrated more rapid elimination of the organism.

Plasma infusion or plasmapheresis has been proposed for patients suffering severe manifestations of HUS with serious CNS involvement. It is specifically contraindicated in those with pneumococcal-associated HUS as it could exacerbate the disease. Treatment in this epidemic included plasma exchange in most of the adult patients, as well as the use of eculizumab.

Most patients with diarrhea-associated HUS recover completely with little risk of long-term sequelae. Patients with hypertension, any level of renal insufficiency, or residual urinary abnormalities persisting a year after an episode of diarrhea-positive HUS (particularly significant proteinuria) require careful follow-up. Patients who have recovered completely with no residual urinary abnormalities after 1 year, are unlikely to have long-term sequelae. Because of some report of late sequelae in such patients, annual examinations with a primary physician are still warranted.

More than 90% of the patients will survive with aggressive management of acute renal failure in acute phase. These recover back to normal renal functions. Treatment involves anticoagulants and primarily heparin. Fibrinolytic therapy will help to dissolve intrarenal thrombi. Plasmapheresis and/or administration of fresh-frozen plasma has been recommended.

Eculizumab is an anti-C5 antibody that inhibits complement activation, a pathway that contributes to active disease in some forms of atypical familial HUS; this pathway may contribute to the process in STEC (Shiga-like toxin producing *E. coli*)–HUS. Eculizumab is FDA approved for the treatment of atypical HUS.

While initial reports suggested that eculizumab provided benefit in patients with diarrhea-associated HUS, subsequent systematic analysis

showed no benefit from either plasma exchange or eculizumab.

In enteritis-related (D+) cases, no specific therapy has been beneficial. Anticoagulation, antiplatelet and fibrinolytic agents, infusion of fresh-frozen plasma and plasma exchange, administration of vitamin E (for its antioxidant action) and infusion of immune globulin are not effective. Adequate supportive care including early and repeated dialysis to prevent and treat complications of renal failure, correction of anemia, control of hypertension, prevention and treatment of infections and nutritional support are the mainstay of management.

Neurological dysfunction and hypertension may result from increased intracranial pressure or cerebral microangiopathy with normal intracranial pressure. A careful evaluation is necessary with CT scanning. In postdysenteric cases, prolonged dysentery and occasionally its surgical complications interfere with oral feeding and lead to severe malnutrition. Parenteral nutrition, modified to the requirements of acute renal failure, may be instituted.

Peritoneal dialysis not only controls the manifestation of uremic state but also promotes the recovery by removing an inhibitor, i.e., plasminogen activates inhibitor of fibrinolysis from the circulation, thus allowing endogenous fibrinolytic mechanisms to dissolve vascular thrombi. Recurrence of the disease is rare.

## PROGNOSIS

With optimal management most patients with D+ HUS recover. The death rate in the acute stage is about 5–10%, from infections and serious complications especially of the CNS. Significant return of renal function seldom occurs in those with thrombotic microangiopathy of majority of the glomeruli or extensive renal cortical necrosis. Almost 30–40% patients who recover from the acute illness are left with impaired renal function or persistent urinary abnormalities.

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# Nephrotic Syndrome

## PRESENTING COMPLAINTS

A 3-year-old boy was brought with the complaints of:

- Irritable since 3 weeks
- Not taking feeds since 3 weeks
- Swelling of the face and limb since 10 days
- Decrease urine output since 10 days

## History of Presenting Complaints

A 3-year-old boy was brought to the hospital with history of swelling in face and limbs. Mother also complained that the child was passing decreased amount of urine. Mother had noticed that her son was not well since almost 3 weeks. In the beginning she had noticed that the boy used to be more irritable and was not taking food at all. After 1 week mother noticed swelling of face, especially around the eye. The swelling used to be more in morning and used to disappear as day passes on.

Later mother noticed that swelling started to appear all over the body. The mother also noticed that child was not passing sufficient amount of urine as he was passing previously. There was no history of increased frequency of micturition. There was no history of burning sensations of micturition. There was no history of allergy or insect bite.

## Past History of the Patient

He was the second sibling of nonconsanguineous marriage. He was born at full term by normal delivery. He cried immediately after delivery. There was no significant postnatal event. He was on breast milk immediately after delivery. His developmental milestones were normal. He had been completely immunized. His performance at school was good.

## EXAMINATION

The boy was moderately built and moderately nourished. Anthropometric measurements included, the height was 106 cm (80th centile), and the weight was 16 kg (95th centile). He was afebrile, pulse rate was 110 per minute, and the respiratory rate was 22 per minute. Blood pressure recorded was 70/50 mm Hg. There was no pallor, there was generalized edema. Edema was pitting in nature.

Per abdomen examination revealed presence of abdominal wall edema. There was no free fluid and no organomegaly. Respiratory system revealed absence of breath sounds on right lower lobe. It was stony dull to percuss. Cardiovascular system was normal.

## INVESTIGATION

Hemoglobin	: 12.2 g/dL
TLC	: 7,600 cells/cu mm
ESR	: 36 mm in the 1st hour
AEC	: 540 cells/cu mm
Serum cholesterol	: 300 mg/dL
Triglycerides	: 50 mg/dL

### CASE AT A GLANCE

#### Basic Findings

Height	: 106 cm (80th centile)
Weight	: 16 kg (95th centile)
Temperature	: 38°C
Pulse rate	: 110 per minute
Respiratory rate	: 22 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Generalized swelling
- Decreased amount of urine
- Tiredness

##### Examination

- Anasarca
- Increased weight
- Absence of breath sounds

##### Investigation

- Cholesterol: Increased
- Triglycerides: Decreased
- Serum albumin: Decreased
- Serum complement: Decreased
- Urine albumin: +++



Serum albumin	: 3 g/dL
Urine	: Albumin +++ Sugar—Nil Microscopy—Normal

## DISCUSSION

Here the boy has presented with the history of generalized edema, oliguria and presence of protein in urine suggests nephrotic syndrome. The diagnosis is supported by increased level of cholesterol and decreased level of triglycerides. Serum protein levels are decreased.

Nephrotic syndrome is a common renal disease. It is characterized by massive proteinuria, hypoalbuminemia and edema. Hyperlipidemia is usually associated with hematuria, hypertension and renal functional impairment. Heavy proteinuria is the basic abnormality leading to hypoproteinemia. The resultant fall in plasma oncotic pressure is responsible for hypovolemia. This stimulates aldosterone functions which in turn enhances sodium retention.

Nephrotic syndrome is the clinical manifestation of glomerular diseases associated with heavy (nephrotic-range) proteinuria. Nephrotic range proteinuria is defined as proteinuria  $>3.5$  g/24 h or a urine protein: creatinine ratio  $>2$ . The triad of clinical findings associated with nephrotic syndrome arising from the large urinary losses of proteins are, hypoalbuminemia ( $<2.5$  g/dL), edema, and hyperlipidemia (cholesterol  $>200$  mg/dL).

Nephrotic syndrome (NS) is not a disease but a constellation of clinical findings common to several glomerular disorders. By definition, it comprises proteinuria greater than 50 mg/kg/24 h (40 mg/m/h or a urinary protein-to-creatinine ratio 2.0 mg/mg), hypoalbuminemia (serum albumin  $<3.0$  g/dL), and hyperlipidemia (elevated very-low-density lipoprotein, intermediate-density lipoprotein, low-density lipoprotein, and triglycerides).

## ETIOLOGY

Most children with nephrotic syndrome have a form of primary or idiopathic nephrotic syndrome. Glomerular lesions associated with idiopathic nephrotic syndrome include minimal change disease (the most common), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, C3 glomerulopathy, and membranous nephropathy. These etiologies have different age distributions. Nephritic syndrome may also be secondary to systemic diseases such as systemic lupus erythematosus, Henoch-Schönlein purpura, malignancy (lymphoma and leukemia), and

infections (hepatitis, HIV, and malaria). Rarely the disorder may be congenital as in syphilis and other intrauterine infections, and Finnish type of nephrotic syndrome.

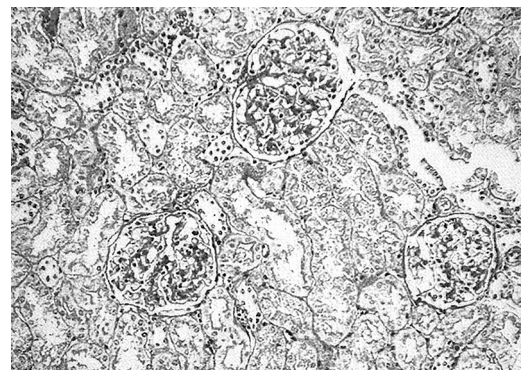
The clinical and biochemical features of nephritic syndrome result from heavy proteinuria (more than 40 mg/m<sup>2</sup>/h to 1 g/m<sup>2</sup>/24 h). Hypoalbuminemia, lowered plasma oncotic pressure and edema follow sustained loss of large amounts of protein in urine. Hyperlipidemia and other abnormalities such as raised plasma aldosterone and antidiuretic hormone levels are prominent in patients having massive proteinuria and anasarca.

## PATHOLOGY

In minimal change nephrotic syndrome (MCNS) (approximately 85% of total cases of nephrotic syndrome in children), the glomeruli appear normal or show a minimal increase in mesangial cells and matrix (**Fig. 1**). Findings on immunofluorescence microscopy are typically negative, and electron microscopy simply reveals effacement of the epithelial cell foot processes. More than 95% of children with minimal change disease respond to corticosteroid therapy.

Mesangial proliferation is characterized by a diffuse increase in mesangial cells and matrix on light microscopy. Immunofluorescence microscopy might reveal trace to 1+ mesangial IgM and/or IgA staining. Electron microscopy reveals increased numbers of mesangial cells and matrix as well as effacement of the epithelial cell foot processes. Approximately 50% of patients with this histologic lesion respond to corticosteroid therapy.

In focal segmental glomerulosclerosis (FSGS), glomeruli show lesions that are both focal (present only in a proportion of glomeruli) and



**Fig. 1:** Histological picture—minimal change nephrotic syndrome.

(For color version see Plate 2)

segmental (localized to >1 intraglomerular tufts). The lesions consist of mesangial cell proliferation and segmental scarring on light microscope.

Idiopathic nephrotic syndrome can be clearly separated into minimal change steroid responsive type. Others with significant glomerular histological lesions are mostly nonresponsive to prednisolone.

Heavy proteinuria is almost due to “glomerular” cause, following alterations of the selective properties of the glomerular capillary wall. As a result proteins that are not normally filtered, or filtered in very small amounts such as albumin pass readily into the urinary space and are excreted in the urine.

## **PATHOGENESIS**

### **Role of the Podocyte**

The underlying abnormality in nephrotic syndrome is an increased permeability of the glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia. The podocyte plays a crucial role in the development of proteinuria and progression of glomerulosclerosis. The podocyte is a highly differentiated epithelial cell located on the outside of the glomerular capillary loop. Foot processes are extensions of the podocyte that terminate on the glomerular basement membrane. The foot processes of a podocyte interdigitate with those from adjacent podocytes and are connected by a slit called the slit diaphragm. The podocyte functions as structural support of the capillary loop, is a major component of the glomerular filtration barrier to proteins, and is involved in synthesis and repair of the glomerular basement membrane. The slit diaphragm is one of the major impediments to protein permeability across the glomerular capillary wall. Slit diaphragms are not simple passive filters—they consist of numerous proteins that contribute to complex signaling pathways and play an important role in podocyte function. Important component proteins of the slit diaphragm include nephrin, podocin, CD2AP, and alpha-actinin 4. Podocyte injury or genetic mutations of genes producing podocyte proteins may cause nephrotic-range proteinuria.

In idiopathic, hereditary, and secondary forms of nephrotic syndrome, there are immune and nonimmune insults to the podocyte that lead to foot process effacement of the podocyte, a decrease in number of functional podocytes, and altered slit diaphragm integrity. The end result is increased protein “leakiness” across the glomerular capillary wall into the urinary space.

### **Role of the Immune System**

Minimal change nephrotic syndrome (MCNS) may occur after viral infections and allergen challenges. MCNS has also been found to occur in children with Hodgkin lymphoma and T-cell lymphoma. That immunosuppression occurs with drugs such as corticosteroids and cyclosporine provides indirect additional evidence that the immune system contributes to the overall pathogenesis of the nephrotic syndrome.

In MCNS, light microscopy does not disclose significant abnormalities and glomerular deposits of immune reactants are not seen on immunofluorescence examination. Serum levels of complement (C3) are normal and circulating immune complexes are absent. There is indirect evidence that immunologic mechanisms may be involved in the pathogenesis of MCNS.

The remissions that occasionally follow measles, presence of allergy in some cases, and response to immunoactive agents (corticosteroids, immunosuppressive and immunomodulatory drugs) suggest an underlying immune dysfunction.

In MCNS, urinary protein mainly consists of albumin, whereas with significant glomerular lesions larger protein molecules (IgG, other globulins) are also detected. The amount of urinary protein excretion in MCNS is also related to the level of serum albumin. With prolonged heavy loss of protein, the serum levels fall to very low levels and thus the total amount of urine protein loss declines. While hypoalbuminemia essentially results from heavy urinary losses, increased gastrointestinal losses and perturbed protein metabolism may also contribute.

Hyperlipidemia is due to increased hepatic synthesis of beta-lipoprotein and decreased lipoprotein lipase activity. Multiple factors are responsible for hypercoagulable state. Blood viscosity secondary to hyperlipidemia, platelet adhesiveness, altered coagulation factors and clotting inhibitors, increased fibrinogen, and decreased antithrombin levels are responsible for hypercoagulable state.

## **CLINICAL FEATURES (FIG. 2)**

### **Edema (Figs. 3A and B)**

Edema is the most common presenting symptom of children with nephrotic syndrome. Despite its almost universal presence, there is uncertainty as to the exact mechanism of edema formation. There are two opposing theories, the underfill hypothesis and the overfill hypothesis, that have

been proposed as mechanisms causing nephrotic edema.

The underfill hypothesis is based on the fact that nephrotic-range proteinuria leads to a fall in the plasma protein level with a corresponding decrease in intravascular oncotic pressure. This leads to leakage of plasma water into the interstitium, generating edema. As a result of reduced intravascular volume, there is increased secretion of vasopressin and atrial natriuretic factor, which, along with aldosterone, result in increased sodium and water retention by the tubules. Sodium and water retention therefore occur as a consequence of intravascular volume depletion.

This hypothesis does not fit the clinical picture of some patients with edema caused by nephrotic

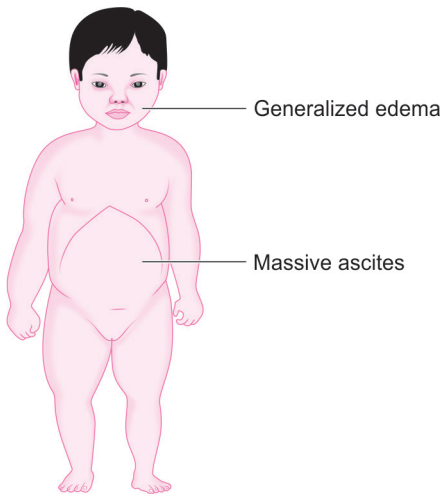
syndrome who have clinical signs of intravascular volume overload, not volume depletion. Treating these patients with albumin alone may not be sufficient to induce a diuresis without the concomitant use of diuretics. Also, reducing the renin-aldosterone axis with mineralocorticoid receptor antagonists does not result in a marked increase in sodium excretion. With the onset of remission of MCNS, many children will have increased urine output before their urinary protein excretion is measurably reduced.

The overfill hypothesis postulates that nephrotic syndrome is associated with primary sodium retention, with subsequent volume expansion and leakage of excess fluid into the interstitium. There is accumulating evidence that the epithelial sodium channel in the distal tubule may play a key role in sodium reabsorption in nephrotic syndrome. The clinical weaknesses of this hypothesis are evidenced by the numerous nephrotic patients who present with an obvious clinical picture of intravascular volume depletion: low blood pressure, tachycardia, and elevated hemoconcentration. Furthermore, amiloride, an epithelial sodium channel blocker, used alone is not sufficient to induce adequate diuresis.

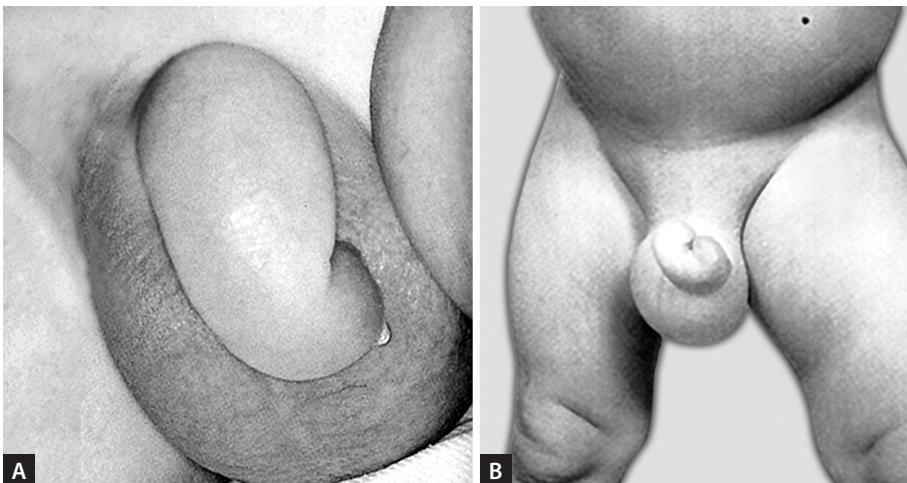
The goal of therapy should be a gradual reduction of edema with judicious use of diuretics, sodium restriction, and cautious use of intravenous albumin infusions, if indicated.

### Hyperlipidemia

There are several alterations in the lipid profile in children with nephrotic syndrome, including an increase in cholesterol, triglycerides, low-density



**Fig. 2:** Clinical features.



**Figs. 3A and B:** Generalized edema.

lipoprotein, and very-low-density lipoproteins. The high-density lipoprotein level remains unchanged or is low. Hyperlipidemia is thought to be result of increased synthesis as well as decreased catabolism of lipids.

## Increased Susceptibility to Infections

Children with nephrotic syndrome are especially susceptible to infections such as cellulitis, spontaneous bacterial peritonitis, and bacteremia. This occurs as a result of many factors, particularly hypoglobulinemia as a result of the urinary losses of immunoglobulin (Ig) G. In addition, defects in the complement cascade from urinary loss of complement factors (predominantly C3 and C5), as well as alternative pathway factors B and D, lead to impaired opsonization of microorganisms.

Children with nephrotic syndrome are at significant increased risk for infection with encapsulated bacteria and in particular, pneumococcal disease. Spontaneous bacterial peritonitis presents with fever, abdominal pain, and peritoneal signs. Although *Pneumococcus* is the most frequent cause of peritonitis, gram-negative bacteria also are associated with a significant number of cases. Children with nephrotic syndrome and fever or other signs of infection must be evaluated aggressively, with appropriate cultures drawn and should be treated promptly and empirically with antibiotics. Peritoneal leukocyte counts >250 are highly suggestive of spontaneous had peritonitis.

## Hypercoagulability

Nephrotic syndrome is a hypercoagulable state resulting from multiple factors: vascular stasis from hemoconcentration and intravascular volume depletion, increased platelet number and aggregability and changes in coagulation factor levels. There is an increase in hepatic production of fibrinogen along with urinary losses of antithrombotic factors such as antithrombin III and protein S. Deep venous thrombosis may occur in any venous bed, including the cerebral venous sinus, renal vein, and pulmonary veins. The clinical risk is low in children (2–5%) compared to adults, but has the potential for serious consequences.

## CLINICAL MANIFESTATIONS

The NS of childhood has been divided into three broad groups: congenital/infantile, primary (inherited or idiopathic), and secondary. Only 10–15% of children have an identifiable secondary cause for their NS.

Congenital NS is defined as heavy proteinuria, hypoproteinemia, and edema starting within 3 months after birth. It is rare. Cases are caused either by genetic defects, especially nephrin and podocin or by a perinatal infection. The Finnish type of congenital NS is caused by a nephrin gene mutation and is not accompanied by extrarenal malformations. Most of these children are born prematurely, with a birth weight ranging between 1.5 kg and 3.5 kg. The placental weight is more than 25% of the newborn weight in practically all cases.

In congenital nephrotic syndrome, renal histology shows cystic tubular dilatation as the prominent feature. With increasing edema urine output may fall. The blood pressure is usually normal. Infection may be present. Hydrothorax and hydrocele may be present.

Proteinuria begins in utero and is detectable in the first urine sample after birth. Microscopic hematuria and normal creatinine values during the 1st month are typical. Heavy protein loss (up to 100 g/L) results in oliguria and severe edema if not treated. Hyperlipidemia, hypothyroidism, and hypogammaglobulinemia are present, due to urinary losses of lipoproteins, thyroid-binding globulins, and immunoglobulin.

By ultrasound, the kidneys are large: with increased cortical echogenicity and indistinct corticomedullary borders. The glomerular histopathology can vary and include minimal change, mesangial expansion, focal segmental glomerulosclerosis, or diffuse mesangial sclerosis, and the findings overlap in different entities. If congenital infections are ruled out, genetic analysis is the preferred method for establishing a definitive diagnosis.

For congenital NS, immunosuppression is not recommended. Conservative management of edema with sodium and fluid restriction and intermittent IV albumin and loop diuretics can usually keep these patients out of the hospital. The management of these patients also includes a hypercaloric diet, thyroid hormone replacement, monitoring for thrombotic episodes, and prompt management of infectious complications.

The outcome of these patients without major extrarenal manifestations is comparable with those of other patient groups after kidney transplantation. Judicious use of ACE is and indomethacin to limit glomerular filtration and subsequent protein losses can allow for adequate growth until the children are large enough to get a kidney transplant. However, other patients require unilateral or bilateral nephrectomy and chronic dialysis as a bridge to kidney transplant.



Primary NS is the occurrence of the constellation of clinical findings that define NS in the absence of an identifiable causative agent or disease. Primary NS is classified into four categories based on biopsy findings: MCNS, MCNS with proliferative changes, focal segmental glomerulosclerosis (FSGS), and membranous nephropathy (MN). Although it is still debated, one theory is that MCNS and FSGS represent different ends in the spectrum of the same disease rather than distinct disorders. From a prognostic perspective, the histologic pattern is less important than is the responsiveness to corticosteroids. Most children with steroid-sensitive-disease have MCNS, so patients with new-onset NS do not undergo routine kidney biopsy at the time of diagnosis.

The idiopathic nephrotic syndrome is more common in boys than in girls (2:1) and most commonly appears between the ages of 2 and 6 years. However, it has been reported as early as 6 months of age and throughout adulthood. MCNS is present in 85–90% of patients <6 years of age.

The initial episode of idiopathic nephrotic syndrome, as well as subsequent relapses, usually follows minor infections and uncommonly, reactions to insect bites, bee stings.

Most patients (95%) initially present with dependent edema that is most obvious in the eyelids, scrotum, and labia. Early morning swelling of the eyelids (periorbital edema) is a common occurrence. The onset is insidious with swelling around the eyes and facial puffiness. In some cases, an upper respiratory tract infection may be associated. The swelling gradually increases to involve the extremities and abdomen and if untreated may become massive. Mild diarrhea is common, probably due to intestinal edema.

Occasionally, generalized swelling over the body may develop acutely and be associated with gross hematuria and oliguria. Such cases present a mixed picture of nephritic syndrome and acute nephritis. They would require urgent detailed investigations including a renal biopsy.

Nephrotic syndrome can initially be misdiagnosed as an allergic disorder because of the periorbital swelling that decreases throughout the day. With time, the edema becomes generalized, with the development of ascites, pleural effusions, and genital edema. Anorexia, irritability, abdominal pain and diarrhea are common. Important features of minimal change idiopathic nephrotic syndrome are the absence of hypertension and hematuria (the so-called nephritic features).

Blood pressure should be repeatedly recorded with appropriate cuff with massive edema. It may

be elevated. Hypovolemia stimulates several vasoconstricting mechanisms that lead to hypertension. The blood pressure level returns to normal with remission. Features of systemic disorder, i.e., fever, joint pain, hepatosplenomegaly causing secondary nephritic syndrome should be looked for.

Several factors may contribute to the increased risk of having cardiovascular disease and stroke; they include hypertension, the use of steroids, systemic inflammation, and the atherogenic plasma lipid profile. In particular, plasma cholesterol and lipoprotein levels are high.

The patients have increased susceptibility to bacterial infection. Peritonitis is frequently seen. Most of the time it is because of *Pneumococcus*. Hypercoagulable state produces renal vein thrombosis.

#### ESSENTIAL DIAGNOSTIC POINTS

- Proteinuria
- Hypoalbuminemia
- Edema
- Hyperlipidemia
- Hematuria

#### DIAGNOSIS

The child should be examined to detect any associated infection. Blood pressure should be repeatedly measured with appropriate sized cuff. In MCNS the blood pressure is normal but occasionally in patients with massive edema it may be elevated.

It is likely that hypovolemia in such cases stimulates several vasoconstricting mechanisms that lead to hypertension. The blood pressure levels return to normal with remission. Features of a systemic disorder (fever, rash, joint pains, hepatosplenomegaly, lymphadenopathy), causing secondary nephritic syndrome, should be looked for.

#### Urinalysis

The diagnosis of nephrotic syndrome is confirmed by urinalysis with first morning urine protein:creatinine ratio and serum electrolytes, blood urea nitrogen, creatinine, albumin, and cholesterol levels.

The urinalysis reveals 3+ or 4+ proteinuria, and microscopic hematuria present in 20% of children. Measurement of 24 hours urinary protein is not essential. Protein excretion of more than 4 mg/m<sup>2</sup>/h on a timed urine collection is considered abnormal. Children with nephrosis it exceeds more than 40 mg/m<sup>2</sup>/h. A urine protein/urine creatinine ratio



of more than 0.5 in children below 2 years old and of more than 0.2 in older children is considered significant. A spot urine protein creatinine ratio should be  $>2.0$ .

Careful and repeated microscopic examination of persistent microscopic hematuria suggests the likelihood of significant renal histologic lesion. Urine should be cultured to exclude urinary tract infection. Hyaline and granular casts may be present.

## Blood Examination

Blood is examined for the levels of urea, creatinine, electrolytes, proteins and cholesterol. In MCNS blood urea levels are within normal range (unless the edema is massive with associated oliguria); elevated levels suggest the presence of significant renal histologic lesions. The level of serum albumin is decreased below 2.5 g/dL and that of cholesterol increased above 250 mg/dL. The severity of these abnormalities is related to the duration of heavy proteinuria. Severe anasarca and massive edema are often associated with serum albumin level of below 1.5 g/dL and cholesterol more than 500 mg/dL.

Serum sodium levels are occasionally decreased, suggesting pseudohyponatremia related to profound hyperlipidemia. Low serum sodium levels in these situation do not require correction, Serum IgG levels are usually low and those of IgM are raised. Serum C3 levels are decreased in a significant proportion of patients with membranoproliferative GN.

An X-ray film of chest and a Mantoux test should be done. An ultrasound evaluation of kidney and urinary tract should also be performed.

## Indications for Renal Biopsy

- Persistent hematuria, high blood urea or creatinine
- Who fail to get remission with 2–4 weeks of daily treatment with prednisolone
- Focal segmental glomerulosclerosis
- Mesangial proliferative glomerulonephritis
- Membrane proliferative glomerulonephritis

### GENERAL FEATURES

- Insidious onset
- Oliguria
- Albuminemia

## DIFFERENTIAL DIAGNOSIS

- Congestive cardiac failure
- Angioneurotic edema

- Kwashiorkor
- Malabsorption syndrome
- Filariasis
- Glomerulonephritis
- Urinary tract infection

### LABORATORY SALIENT FINDINGS

- Hypoalbuminemia
- Hyperlipidemia
- Proteinuria
- Hematuria

## TREATMENT

Treatment includes management of initial episode, management of relapse and management of complications.

### Management of Initial Episode

Clinical and laboratory evaluation identifies children likely to have MCNS. In such cases a standard course of prednisolone is instituted. The onset of nephritic syndrome beyond the age of 8–10 years, presence of gross or persistent microscopic hematuria, hypertension and raised serum creatinine levels indicate the presence of a significant glomerular lesion. Renal biopsy should be carried out in these patients.

Children with presumed MCNS, prednisone or prednisolone should be administered as a single daily dose of 60 mg/m<sup>2</sup>/day or 2 mg/kg/day to a maximum of 60 mg daily for 4–6 weeks followed by alternate-day prednisone (starting at 40 mg/m<sup>2</sup> qid or 1.5 mg/kg qid) for a period ranging from 8 weeks to 5 months, with tapering of the dose. When planning the duration of steroid therapy, the side effects of prolonged corticosteroid administration must be kept in mind. Treatment with corticosteroids results in abolition of proteinuria (remission) usually by 10–14 days, diuresis and loss of edema.

The parents should be given an explanation of the condition and the importance of compliance with the treatment. The side effects of prednisolone and the need for prolonged initial therapy should be made clear.

Infusion of 25% albumin solution in dose of 0.5–1 g/kg of albumin over 1–2 hours and followed by a potent diuretic such as furosemide (1–4 mg/kg/day in two divided doses) alone or with an aldosterone antagonist/ spironolactone (2–3 mg/kg/day in two divided doses) can be used to induce diuresis in a child not responding to furosemide alone.

Children with their first episode of nephrotic syndrome and mild to moderate edema may be

managed as outpatients. Children with onset of uncomplicated nephrotic syndrome between 1 and 8 years of age are likely to have steroid-responsive MCNS, and steroid therapy may be initiated without a diagnostic renal biopsy. Children with features that make MCNS less likely (gross hematuria, hypertension, renal insufficiency, hypocomplementemia, or age <1 year and >12 years) should be considered for renal biopsy before treatment.

Approximately 80–90% of children respond to steroid therapy. Response is defined as the attainment of remission within the initial 4 weeks of corticosteroid therapy. Remission consists of a urine protein:creatinine ratio of <0.2 or <1+ protein on urine dipstick for 3 consecutive days. The vast majority of children who respond to prednisone therapy do so within the first 5 weeks of treatment.

Most patients respond to prednisolone with complete disappearance of proteinuria by the end of the 2nd week of therapy and only a minority will respond after 4 weeks of treatment. Persisting proteinuria after 4–6 weeks of therapy defines initial steroid resistance.

Children in their first episode should be treated for at least 3 months, with an increase in benefit being demonstrated for up to 6–7 months is likely to result in a longer remission and fewer relapses without an increase in serious adverse events. Based on these observations, a regimen a prolonged duration of alternate day therapy with tapering doses of prednisolone will be adopted.

In a very small proportion of cases there may be no relapse or a single relapse. In most cases, however, relapses and remissions over a varying period of time are the rule. Relapses are more frequent in younger children. Various terms used to describe the patterns of response of nephrotic syndrome to a standard regimen of corticosteroids are listed in **Table 1**.

Of patients who respond to prednisolone 25–40% have infrequent relapses (an occasional patient may get one or two relapses followed by permanent cure), 40% frequent relapses and the remainder show steroid dependence.

#### INDICATIONS FOR SECONDARY THERAPY

- Not responding initial dose of prednisolone
- Frequent relapsers
- Affected by side effects steroids
- Nonresponders to prednisolone during relapses

The current definition of steroid-responsive-ness is response within 8 weeks. Once the urine becomes negative for protein, the prednisone is

**TABLE 1:** Pattern of response to corticosteroid therapy.

Remission	Protein-free urine (urine protein negative or trace or <4 mg/ m <sup>2</sup> /h) for 3 consecutive days
Relapse	Proteinuria (urine protein 3+ or more) for 3 consecutive days
Infrequent relapse	A responder who relapses but has three or less relapses within 1 year
Frequent relapse	A relapser who has two relapses or more within 6 months of the initial episode or more than three relapses within any 12-month period
Steroid dependent	Occurrence of two consecutive relapses during alternate day prednisolone therapy or within 2 weeks of its discontinuation
Initial resistance	Absence of remission despite 6 weeks of initial steroid treatment
Late responder	Patient with initial resistance, who responds at some time after initial treatment
Late resistance	Initial responder, who subsequently fails to respond to steroid therapy

switched to alternate days and tapered over the course of 6 weeks or longer. The total duration of daily and alternate-day steroid therapy used to treat the initial episode influences the subsequent relapse rate. However, three recent well-designed clinical trials showed no significant reduction in the risk of having a relapse when extending the therapy past 3 months. Alternate-day dosing of prednisone during the taper has been shown in pediatrics to cause less growth suppression.

Almost 50% of children with steroid-sensitive nephrotic syndrome (SSNS) experience several relapses. There is no agreement on a standard protocol for treating relapses. A commonly used protocol is prednisone 60 mg/day until the urine is free of protein for 5–7 days; this is followed by alternate-day therapy that is tapered over several weeks.

### Prednisolone Dependence

About 20% patients respond to prednisolone but require its continued daily administration for maintenance of remission. They promptly relapse when either the dosage of prednisolone is reduced or the medication stopped. Some of these patients may be managed with relatively higher doses of prednisolone given on alternate days.

When a child with NS develops two consecutive relapses during steroid therapy or when the ability to achieve and/or remain in remission from NS

requires administration of corticosteroids (relapse within 14 days of its cessation), then the child is considered to be steroid-dependent. Patients with steroid-dependent nephrotic syndrome (SDNS) may also fit the definition for having frequently relapsing nephrotic syndrome (FRNS), and similarly to FRNS, the potential adverse effects of the cumulative steroid doses required to maintain remission exceed presumed benefits of achieving remission of NS. MCNS is the most common cause of SDNS. Before initiating steroid-sparing therapies, a biopsy may be performed.

## Steroid Resistance

Steroid resistance is defined as the failure to achieve remission after 8 weeks of corticosteroid therapy.

Steroid-resistant nephrotic syndrome (SRNS) is defined as a failure to achieve remission after 6–8 weeks of full-dose daily prednisone. Approximately 15–20% of children with idiopathic NS will develop disease that is resistant to steroids. In addition, a small subset of patients who initially are responsive to steroids do evolve into having SRNS.

Because MCNS is less common and FSGS is more common in this population, a biopsy is recommended for steroid-resistant patients prior to initiating alternative therapies. Genetic testing also is performed by many nephrologists for patients with SRNS, especially those who present at younger than 2 years of age or when there is a positive family history of NS.

Children with steroid-resistant nephrotic syndrome require further evaluation, including a diagnostic kidney biopsy, evaluation of kidney function, and quantitation of urine protein excretion (in addition to urine dipstick testing). Steroid-resistant nephrotic syndrome is usually caused by FSGS (80%), MCNS, or membranoproliferative glomerulonephritis.

Steroid-resistant nephrotic syndrome, and specifically FSGS, is associated with a 50% risk for end-stage kidney disease within 5 years of diagnosis if patients do not achieve a partial or complete remission. Children reaching end-stage kidney disease have a greatly reduced life expectancy compared to their peers.

A renal biopsy is carried out in all steroid resistant patients to determine the pattern of the underlying glomerular lesion. Minimal change, mesangial proliferative GN, focal segmental glomerulosclerosis (FSGS), membranoproliferative GN (MPGN) and membranous nephropathy account for most of these cases.

A small proportion of patients with MCNS have initial steroid resistance. Of these almost 40% respond to treatment with a 12-week course of cyclophosphamide (2–2.5 mg/kg/day). Those who subsequently relapse may respond to corticosteroids.

## RELAPSE OF NEPHROTIC SYNDROME

Relapse of nephrotic syndrome is defined as a urine protein:creatinine ratio of >2 or protein on urine dipstick testing for 3 consecutive days. Relapses are common, especially in younger children, and are often triggered by upper respiratory or gastrointestinal infections. Relapses are usually treated in a manner similar to the initial episode, except that daily prednisone courses are shortened.

## Frequent Relapsers (FRNS)

If a child with NS experiences frequent relapses (two or more relapses within 6 months of initial response or four or more relapses within any 12-month period), then the potential adverse effects of cumulative steroid doses required to achieve remission begin to exceed the presumed benefits of maintaining remission of the NS.

## Treatment of Relapse

An upper respiratory infection, or occasionally some other infection, often precipitates a relapse. Sometimes mild to moderate proteinuria occurs with such infections. Urine protein does not usually exceed 2+ (although occasionally even 3+/4+ may be observed for 3 or 4 days) and lasts for a week or so. Such brief episodes of spontaneously resolving mild proteinuria may not be regarded as relapses.

The relapse is treated with prednisolone 2 mg/kg daily in two divided doses (single daily dose is equally effective) until the urine is protein free for 3 consecutive days, which usually takes 10–14 days. Thereafter prednisolone is given at a dose of 1.5 mg/kg on alternate days for 4 weeks and then stopped.

## Long-term Alternate Day Prednisolone

Prednisolone given as a single early morning dose on every alternate day for several months is often effective in maintaining a remission or reducing the number of relapses. Thus, a dose of 0.5–0.25 mg/kg on alternate days for 9–12 months or longer should be the initial regimen for children with frequent relapses. It has few side effects and does not seem

to interfere with growth. Breakthrough relapses are treated with the standard therapy of relapse.

### Long-term, Low Dose Daily Prednisolone

A few studies suggest that daily administration of a small dose of prednisolone (0.25 mg/kg/day) or hydrocortisone for 1 year or more may maintain a patient in remission. However, because of concern with physical growth this regimen has not been widely used.

Patients with frequent relapses (FRNS) who show persistence or development of steroid toxicity need treatment with alternative drugs.

The possibility of medication noncompliance, including use of lower than recommended prednisone doses, and the presence of occult infections (dental infections or sinusitis) should always be considered in patients with frequent relapses. Although some nephrologists perform kidney biopsy on children after diagnosis of FRNS, nearly all have proven to be minimal change disease.

In cases of FRNS, the alternate-day dose can be tapered to a “threshold dose” (a dose below which relapses occur) to reduce the number of relapses and the total cumulative dose of steroid therapy. This dose is often in the range of 15–20 mg/kg and is continued for 12–18 months.

Steroid-sparing strategies have also been developed to treat FRNS. One strategy involves alkylating agents such as oral cyclophosphamide for 8–12 weeks, which is generally well tolerated with minimal risk of gonadal toxicity (total cumulative dose <200 mg/kg). Chlorambucil also is effective but is used less widely because of the risk of seizures. The alkylating agent is ideally started after induction of remission (to minimize the risks of developing infections and hemorrhagic cystitis) and is used in combination with low-dose prednisone. Other steroid-sparing strategies used for treatment include a 6-month course of oral MME. B-cell depletion with rituximab, and calcineurin inhibitors.

Patients having frequent relapses and requiring repeated courses of prednisolone often develop serious steroid toxicity. Important side effects include severe cushingoid features (obesity, hirsutism, striae), hypertension, impaired glucose tolerance, posterior subcapsular lenticular opacities, emotional problems and growth retardation. Institution of an alternative regimen is required in patients with frequent relapses. Serious complications of corticosteroid therapy should not be allowed to develop.

As in FRNS, the alternate-day oral corticosteroid can be tapered to the threshold dose.

Other steroid-sparing strategies used for treatment include a 6-month course of B-cell depletion with rituximab, calcineurin inhibitors, and vincristine. Children with SDNS do not respond as well to alkylating agents as does the FRNS subgroup. Patients with SDNS tend to also be medication-dependent to maintain a sustained remission.

A helpful assessment is the steroid threshold, i.e., the minimum corticosteroid dosage at which relapses have occurred. This should not be confused with the dosage used to treat the relapse. The maintenance dose should be continued for a period of 9–12 months or longer provided there are no major side effects.

### Levamisole

Levamisole, an immunomodulatory agent without anti-inflammatory effect, has been successfully employed in patients with frequent relapses and steroid dependence. A dose of 2–2.5 mg/kg administered on alternate days for 1–2 years or longer has been found to be effective in about 50–60% cases, with a marked reduction in the relapse rate. Initially, prednisolone 0.75–1 mg/kg is given along with levamisole, and after a few weeks its dose is gradually decreased. In 20–30% cases prednisolone can be stopped and levamisole alone is sufficient. There is a strong tendency for relapses to recur when levamisole is discontinued.

Neutropenia may occur in 2% of cases, monitoring of blood leukocyte counts is advised every 2–4 months.

### Alkylating Agents: Cyclophosphamide

The role of alkylating agents in treating SRNS is unclear, but a subset of patients will respond, especially those who had at least a partial response to prednisone therapy. Combined treatment with high-dose corticosteroids (oral prednisone with or without intravenous pulse steroids) and alkylating agents have induced a partial or complete remission in 30–60% of patients in some case series, but these protocols are associated with significant morbidity and should be limited to patients with well-preserved kidney function. Even a partial response is associated with a better outcome.

Alkylating agents, chiefly cyclophosphamide and chlorambucil may induce long lasting or rarely permanent remission in children with FRNS, either of these drugs is administered after inducing a remission with the standard prednisolone treatment.

A 12-week course of cyclophosphamide at a dosage of 2–2.5 mg/kg/day along with alternate

day prednisolone (1–1.2 mg/kg) results in prolonged remission in a majority of patients. The results are better in older children. The use of chlorambucil has been more limited than that of cyclophosphamide. The dose of chlorambucil is 0.2–0.3 mg/kg/day along with alternate day prednisolone (1 mg/kg) for 12 weeks. Both of these agents cause leukopenia, nausea and vomiting. Blood examination is done every 2 weeks and if the total white cell count falls below 4000/cu mm the drug is withheld till the counts reach normal levels.

## Cyclosporine

Cyclosporine (CsA) causes specific and reversible inhibition of T-helper lymphocytes. It also inhibits production and release of lymphokines including interleukin-2. CsA is mainly employed in organ transplantation, but it has been found to be effective in a variety of immunologically mediated disorders and in nephritic syndrome.

Cyclosporine A (CsA) is effective in inducing and sustaining remission in 75–80% of patients with SRNS and has had a major impact in a small group of patients debilitated by the disease and by steroid toxicity and in some patients who have had a poor response to cyclophosphamide.

The dose of CsA is 3–5 mg/kg/day (100–150 mg/m<sup>2</sup>/day), which may achieve whole blood trough levels of 150–250 ng/mL. CsA is preferably combined initially with alternate day prednisolone (for 12–20 weeks) and is given for 1 year or longer.

CsA levels must be carefully monitored, and some recommend repeat kidney biopsy to evaluate the degree of interstitial fibrosis if therapy is continued for longer than 18 months. Unfortunately, relapses commonly occur once CsA is discontinued. Mild side effects frequently occur and include hypertension, gingival hypertrophy, and hirsutism.

## Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is a potent, reversible inhibitor of inosine monophosphate dehydrogenase, an enzyme required for de novo purine synthesis. Long-term treatment with this medication appears to be promising in patients with difficult nephritic syndrome, with no risks of nephrotoxicity, hepatotoxicity or neurotoxicity, or cosmetic side effects. The dose of MMF is 20–25 mg/kg/day in two divided doses.

## Other Therapies

Cyclosporine in combination with alternate day prednisolone may induce remission in 60–70%

patients of steroid resistant MCNS and 30–40% of those with FSGS. Most patients who respond do so within 3 months of therapy. The treatment is carried out for 1–2 years. Other drugs that may have some benefit include nitrogen mustard and tacrolimus (FK 506).

Tacrolimus appears to be equally effective, avoids the development of the hirsutism and gingival hypertrophy associated with CsA treatment, and is now more commonly used in many programs. Starting doses of 0.05–0.1 mg/kg/dose twice daily are usually adjusted to achieve goal predose blood levels of 4–10 mg/mL. Steroid- and calcineurin inhibitor-resistant patients rarely respond to the other known immunosuppressant medications, including cytotoxic agents, rituximab, and MMF.

## General Supportive Management

Besides specific therapy, control of edema, prevention and treatment of infections and the general care of the child and management of psychological problems are crucial.

## Dietary Management

Patients with nephrotic syndrome often present with anasarca, either initially or during relapses. They may show evidence of prolonged, severe protein deficiency such as a greatly reduced muscle mass and infections. In such cases a high protein diet should be encouraged along with supplements of vitamins and micronutrients.

There is little doubt that the high protein diet and rise in serum albumin will increase proteinuria, but no evidence to indicate that all ingested protein is lost. Conversely, severe reduction of dietary protein (often advised by indigenous practitioners) decreases proteinuria, at the expense of extreme reduction of serum albumin and muscle mass. In MCNS proteinuria is resolved within 10–14 days with corticosteroid therapy and a high protein diet is continued to replenish body protein.

During daily administration of prednisolone dietary salt should be restricted, to decrease the tendency to hypertension. The 12-week prednisolone regimen may lead to excessive weight gain, and in this period fat intake should be curtailed.

Calcium and vitamin D supplements are required in patients with persistent heavy proteinuria due to steroid resistant nephritic syndrome. Diuretic induced losses of potassium may be replaced by potassium supplements.



## Edema

Children with severe symptomatic edema, including large pleural effusions, ascites, or severe genital edema, should be hospitalized. In addition to sodium restriction (<1500 mg daily), water/fluid restriction may be necessary if the child is hyponatremic. A swollen scrotum may be elevated with pillows to enhance fluid removal by gravity. Diuresis may be augmented by the administration of loop diuretics (furosemide), orally or intravenously, although extreme caution should be exercised. Aggressive diuresis can lead to intravascular volume depletion and an increased risk for acute renal failure and intravascular thrombosis.

When a patient has severe generalized edema with evidence of intravascular volume depletion (e.g., hemoconcentration, hypotension, tachycardia), IV administration of 25% albumin (0.5–1.0 g albumin/kg) as a slow infusion followed by furosemide (1–2 mg/kg/ dose IV) is sometimes necessary.

In MCNS edema occurs due to massive proteinuria, hypoalbuminemia, reduction in plasma oncotic pressure and leakage of fluid into the interstitial space. Hypovolemia and decreased effective arterial volume lead to activation of compensatory mechanisms (e.g., secondary hyperaldosteronism) that result in salt and water retention. Other mechanisms may be responsible in patients with nonminimal lesions and reduced renal function.

Early treatment of relapse and judicious use of diuretics will ensure that the child does not develop more than a slight edema.

## Diuretics

### *Furosemide and Bumetanide*

Furosemide and bumetanide (called loop diuretics) are very potent diuretics with their principal site of action on the thick ascending limb (TAL) of the loop of Henle, where 25–30% of the filtered sodium and chloride is normally reabsorbed.

On oral administration of furosemide, the onset of action is within 1 hour with a peak action between 1 and 2 hours and duration of action of 6–8 hours. With intravenous injection the action starts within 5 minutes, the peak is within 30 minutes and the duration 2 hours.

## Thiazides

Thiazides are organic anions that are also secreted into the proximal nephron. They inhibit sodium

reabsorption in the distal convoluted tubule chiefly by inhibiting the NaCl transporter. They have no action on the ascending limb of Henle. Onset of action is within 2 hours with a peak at 4 hours and the effect persists for 6–12 hours. Side effects include hypokalemia, hyponatremia, hypokalemic alkalosis and hypomagnesemia.

### *Metolazone*

Metolazone belongs to the thiazide class of diuretics. It blocks sodium chloride reabsorption in proximal and early distal nephron sites by unknown mechanisms. Since the major tubular site for phosphate reabsorption is the proximal tubule, the phosphaturia associated with metolazone administration exceeds that with thiazides.

### *Spironolactone*

Spironolactone, a specific pharmacological antagonist of aldosterone, acts through competitive binding to receptors of aldosterone dependent Na-K exchange sites in the principal cells of cortical collecting ducts. Spironolactone is rapidly absorbed.

### *Triamterene and Amiloride*

These potassium-sparing agents block the sodium channel in the principal cell of cortical collecting duct, inhibiting sodium reabsorption.

### *Dyslipidemia*

Dyslipidemia should be managed with a low-fat diet. Dietary fat intake should be limited to <30% of calories with saturated fat intake <10% calories. Dietary cholesterol intake should be <300 mg/day.

## Infections

If there is suspicion of infection, a blood culture should be drawn prior to starting empiric antibiotic therapy. In the case of spontaneous bacterial peritonitis, peritoneal fluid should be collected if there is sufficient fluid to perform a paracentesis and sent for cell count, Gram stain, and culture. The antibiotic provided must be of broad enough coverage to include *Pneumococcus* and gram-negative bacteria. A third-generation cephalosporin is a common choice of IV antibiotic.

### *Thromboembolism*

Studies to delineate a specific underlying hypercoagulable state are recommended. Anticoagulation therapy in children with thrombotic events

appears to be effective—heparin, low-molecular-weight heparin, and warfarin are therapeutic options.

### *Obesity and Growth*

Glucocorticoids may increase the body mass index in children who are overweight when steroid therapy is initiated, and these children are more likely to remain overweight. Anticipatory dietary counseling is recommended. Growth may be affected in children who require long-term corticosteroid therapy. Steroid-sparing strategies may improve linear growth in children who require prolonged courses of steroids.

### **Complications**

- Massive anasarca with ascites and serious effusions
- Serious infections such as peritonitis and extensive cellulitis
- Flare up of tuberculosis
- Severe hypovolemia that may lead to acute renal failure especially when complicated by gastroenteritis and other infections
- Thrombosis (both arterial and venous) of major vessels, including cerebral venous sinuses

### *Management of Complications*

- *Edema:* It is controlled with salt reduction and oral dose of hydrochlorothiazide (1–2 mg/kg/day) or furosemide. Sometime furosemide along with spironolactone is used.

- *Infection:* Nephrotic state and corticosteroid therapy makes susceptible to infections. This can be with *Streptococcus pneumoniae*, gram-negative organism and varicella, peritonitis, pneumonia and meningitis.
- *Thrombotic complications:* These include renal, pulmonary and cerebral vein thrombosis.
- *Acute renal failure:* Appropriate preventive measures and judicious fluid replacement is required.

## **IMMUNIZATIONS IN CHILDREN WITH NEPHROTIC SYNDROME**

To reduce the risk of serious infections in children nephrotic syndrome, give full pneumococcal vaccination (with 13-valent conjugate vaccine and 23-valent polysaccharide vaccine-influenza vaccination annually to the child and their household tacts; defer vaccination with live vaccines until the prednisone below either 1 mg/kg daily or 2 mg/kg on alternate days.

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# Urinary Tract Infection

## PRESENTING COMPLAINTS

A 4-year-old girl was brought with the complaints of:

- Fever since 2 days
- Abdominal pain since 2 days
- Increased frequency of urine since 1 day

## History of the Presenting Complaints

A 4-year-old girl was brought to the pediatric outpatient department by her mother with the history of fever, abdominal pain and increased frequency of the micturition. Mother had noticed the fever since 2 days of moderate to high degree, no associated chills and rigors. Used to be relieved temporarily by paracetamol. Mother also revealed that her daughter is complaining of the pain in the abdomen. It was diffuse more so in the lower abdomen. She also told her daughter is passing the urine very frequently. Amount of the urine used to

be small. She was crying while passing the urine. Mother had also noticed that her daughter had nausea.

## Past History of the Patient

She was the only sibling of the nonconsanguineous marriage. She was born at term with the normal vaginal delivery. The birth weight was 3 kg. She started taking the breast milk immediately. There was no significant postnatal event. She was discharged on third day. Child was exclusively on breast milk for the first 3 months. Later weaning was started with cereals and vegetables. Child was on family food by 18 months. Her development milestones were normal. She had been immunized completely.

## EXAMINATION

Child was moderately built and nourished. She was looking sick. Signs of moderate dehydration were present. Anthropometric measurements included the height 100 cm (75th centile) and weight was 15 kg (50th centile).

The child was febrile 39°C pulse rate was 126 per minute. The respiratory rate was 22 per minute. Blood pressure recorded was 70/50 mm Hg. There was no pallor, no edema, no clubbing and no lymphadenopathy.

Per abdomen examination revealed diffuse tenderness at the lower abdomen. There was no organomegaly. Bowel sounds were regular. Cardiovascular and respiratory system were normal.

## INVESTIGATION

Hemoglobin	: 11 g/dL
TLC	: 18,000 cells/cu mm
DC	: P <sub>80</sub> L <sub>18</sub> M <sub>2</sub>
ESR	: 20 mm in the 1st hour
Urine routine	: Albumin ++
	Sugar : Nil
	Pus cells : 18–20 cells/HPF
	RBC : 2–4 cells/HPF

### CASE AT A GLANCE

#### Basic Findings

Height	: 100 cm (75th centile)
Weight	: 15 kg (50th centile)
Temperature	: 39°C
Pulse rate	: 126 per minute
Respiratory rate	: 22 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Fever
- Abdominal pain
- Increased frequency of urine
- Nausea

##### Examination

- Febrile
- Sign of mild dehydration
- Abdominal tenderness

##### Investigation

- TLC increased
- Urine: Albumin ++
  - Pus cells : 18–20 cells/HPF
  - RBCs : 2–4 cells/HPF
- Urine culture and sensitivity: Yields *E. coli*

Urine culture  
and sensitivity : Yields *E. coli*  
Ultrasound  
abdomen : NAD

## DISCUSSION

Urinary tract infections (UTIs) imply invasion of urinary tract by pathogens, which may involve the upper or lower tract depending on the infection in the kidney, or bladder and urethra.

Urinary tract infection constitute a common cause of morbidity in association with abnormalities of the urinary tract, contribute to long term complications, including hypertension and chronic renal failure. Prompt detection and treatment of UTI and complicating factors are of utmost importance.

The incidence of UTI in the term neonate is approximately 1% and in the preterm 3%, both with male preponderance (male to female ratio of 5:1) during infancy.

Obstructive lesions may be found in 10% of boys investigated for UTI and 30–40% patients show vesicoureteric reflux (VUR). The occurrence of UTI below 2 years of age, delay in starting treatment and presence of VUR or obstruction are the chief risk factors associated with renal scarring.

## PATHOGENESIS AND PATHOLOGY

The pathogenesis of UTI depends on a complex interaction between bacterial and host-factors. The urinary tract is normally a sterile environment with nearby bacterial reservoirs in the distal urethra, periurethral region, perianal region, perineum, and vagina. With normal hydration and spontaneous voiding, the urinary flow through the distal urethra helps to prevent bacterial ascension into the bladder. Maintenance of normal flora prevents more virulent strains from colonizing the gut and the periurethral area; an individual's microbiome may be influenced by age, hormones, recent antibiotic use, hygiene, or spermicides.

*E. coli* is the most common uropathogen and causes about 80% of all UTIs; other common gram-negative uropathogens include *Klebsiella*, *Proteus*, *Enterobacter*, and *Citrobacter*. Common gram-positive uropathogens include *Staphylococcus saprophyticus*, *Enterococcus*, and rarely, *Staphylococcus aureus*.

Urinary tract infections are caused primarily by colonic bacteria. In girls, 75–90% of all infections are caused by *Escherichia coli*, followed by *Klebsiella* and *Proteus* spp. Although *E. coli* also

the most common organism in males, some series report that in boys older than 1 year of age, *Proteus* is as common a cause as *E. coli*, others report a preponderance of gram-positive organisms in boys *Staphylococcus saprophyticus* and *Enterococcus* are pathogens in both sexes. Adenovirus and other viral infections also can occur, especially as a cause of cystitis with gross hematuria.

*Proteus* and *pseudomonas* are associated with recurrent UTI, instrumentation and nosocomial infections. Pathogens of low virulence and fungi may be causative in patients who are immunocompromised. *Candida albicans* infections are particularly seen in preterm infants.

In the neonatal period, renal parenchymal infection is due to hematogenous spread. Acute bacterial pyelonephritis may cause or follow septicemia. At all other ages, bacteria reach the urethra and bladder through the ascending route and ureters and kidney through VUR. Bacteria infecting the urinary tract generally arise from the bowel.

Nearly all UTIs are ascending infections. The bacteria arise from the fecal flora, colonize the perineum, and enter the bladder via the urethra. In uncircumcised boys, the bacterial pathogens arise from the flora beneath the prepuce. In some cases, the bacteria causing cystitis ascend to the kidney to cause pyelonephritis.

The majority of UTIs are initiated by bacteria that ascend the urethra and adhere to the mucosal lining of the bladder; a hematogenous source that seeds the urinary tract is much less common but is also possible. The pathogenesis of UTI is based in part on the presence of bacterial pili or fimbriae on the bacterial surface. There are two types of fimbriae, type I and type II. Type I fimbriae are found on most strains of *E. coli*. Because attachment to target cells can be blocked by D-mannose, these fimbriae are referred to as mannose sensitive. They have no role in pyelonephritis. The attachment of type II fimbriae is not inhibited by mannose, and these are known as mannose resistant. These fimbriae expressed by only certain strains of *E. coli*. The receptor for type II fimbriae is a glycosphingolipid that is present on both the uroepithelial cell membrane and red blood cells. Because these fimbriae can agglutinate by erythrocytes, they are known as *P. fimbriae*. Bacteria *P. fimbriae* are more likely to cause pyelonephritis.

Following adhesion, the bacteria may invade across the mucosal barrier and trigger an inflammatory host reaction. White blood cells (WBCs) are

then recruited to respond to the bacterial invasion, resulting in leukocytes appearing in the urine (pyuria). The inflammatory response results in the typical symptoms of cystitis including dysuria, urinary frequency, and urgency. Between 76 and 94% of pyelonephritogenic strains of *E. coli* have *P. fimbriae*, compared with 19–23% of cystitis strains.

Bacteria that reach the urinary bladder are expelled with micturition. However, because of very rapid bacterial multiplication normal voiding cannot eliminate all bacteria. A small number may remain in a moist film lining the bladder mucosa and are destroyed by the intrinsic defense of the bladder epithelial cells. Other defense mechanisms include secretory IgA in urine and blood group antigens in secretions that impede bacterial adhesion.

Infected urine then stimulates an immunologic and inflammatory response. The result can cause renal injury and scarring. Children of any age with a febrile UTI can have acute pyelonephritis and subsequent renal scarring, but the risk is highest in those younger than 2 years of age.

Symptomatic UTI occurs when local bladder defense mechanisms are overcome by virulence of invading bacteria. Whenever bladder emptying is not complete and there is residual urine, the likelihood of UTI is increased. Primary disturbances of bladder function with incomplete evacuation are often present in children with recurrent UTI in whom no anatomical abnormalities of the urinary tract or VUR can be demonstrated.

There can be mechanical, anatomic, or structural risk factors that promote UTI. Indwelling catheters breach the separation between urinary tract and colonized body surface. Congenital genitourinary anomalies indicated by dilation anywhere along the urinary tract often present with UTI because there has been obstruction to normal antegrade urine flow. On the other hand, if during gestational development there was abnormal migration of the Wolffian ducts resulting in VUR, VUR increases the risk of pyelonephritis by promoting bacterial ascension to the kidneys.

Throughout childhood, adolescence, and adulthood, females are at higher risk for UTI than males. In contrast, during the early part of the first year of life, boys have a higher incidence of UTI than girls. After the first year of life, the incidence of UTI in males drops and rises in females. Uncircumcised boys have up to 12 times the risk of UTI than circumcised boys. Factors such as dysfunctional voiding, constipation, sexual activity,

and bladder catheterization increase the risk of UTI.

## PREDISPOSING FACTORS

A variety of conditions lead to an increased predisposition to UTI. These include obstructive uropathy, stones in urinary tract, incomplete emptying of bladder with residual urine, constipation and thread worm infestation. UTI are 10 times more common in non-circumcised infants.

The greatly increased incidence of UTI in girls after infancy may be related to the short female urethra, which permits easy entry of bacteria into the bladder. However, uncircumcised boys also have a high incidence of UTI despite their long urethra. Bacterial colonization may be an important factor. Babies born of mothers with bacteriuria during pregnancy develop rapid colonization by uropathogens and have a higher incidence of UTI.

Broad-spectrum antibiotic therapy for minor infections, such as, upper respiratory tract infections, may abolish the normal bacterial flora of perineum and allow colonization by more virulent organisms, thus predisposing to UTI.

### RISK FACTORS FOR URINARY TRACT INFECTION

- Premature infants
- Immunodeficiency disease
- Systemic disease
- Urinary tract abnormalities
- Renal calculi
- Neurogenic bladder
- Voiding dysfunction
- Chronic severe constipation
- Family history of UTI
- Girl less than 5 years with history of UTI

Breastfeeding has been found to protect infants against UTI during the first 6 months of life. Human milk provides antiadhesive factors in the urine and stabilizes intestinal flora with less pathogenic enteropathogens. Bacterial properties play a major role in UTI. Adhesion of bacteria to the epithelial cells is a prerequisite for their further multiplication and induction of inflammation.

## CLINICAL FEATURES (FIG. 1)

The manifestations of UTI are related to the age and the severity of the infection. Features of the physical examination that should be emphasized include (1) an accurate measurement of blood pressure (hypertension may be present in patients who have chronic renal disease), (2) general growth and development (failure to thrive may be a sign of chronic or recurrent UT), and (3) a careful



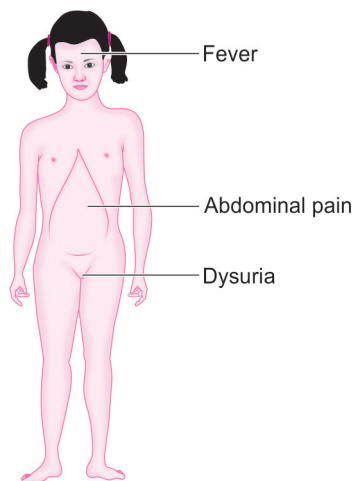


Fig. 1: Clinical features.

abdominal examination which might reveal tenderness or a mass caused by either an enlarged bladder or an obstructed urinary tract). An effort should be made to elicit the finding of costo-vertebral angle tenderness in children of all ages. The perineum should be inspected carefully to search for signs of irritation, scars, signs of trauma, labial adhesions, or evidence of vulvovaginitis. A rectal examination should be considered to detect masses or poor sphincter tone, which might be associated with a neurogenic bladder. The lower back should be observed for any lipoma, sinus, pigmentation, or tuft of hair that may be evidence of an occult myelodysplasia.

### Neonates and Infants

In neonates, acute pyelonephritis presents with features of sepsis such as lethargy, seizures, shock, unstable temperature and persistence of physiological jaundice. Non-specific symptoms including failure to thrive, vomiting, diarrhea may be caused by UTI.

Urine may be foul smelling. In infants, unexplained fever may be the only symptom of acute pyelonephritis. UTI in infants, below 1 year of age is indicative of acute pyelonephritis.

The presence of UTI should be strongly considered in infants and young children, below 2 years of age having unexplained fever. Approximately 3–5% of such children, girls more than boys, with fever and no obvious source of infection on physical examination have UTI. Infants and young children are at higher risk for acute renal injury from UTI. Further the risk of renal damage increases exponentially with the number of such episodes.

### GENERAL FEATURES

- Lethargy
- Seizures
- Shock
- Unstable temperature
- Jaundice
- Burning micturition
- Prolonged voiding
- Hypogastric pain
- Rigors and chills

### Older Children

Dribbling, prolonged voiding, straining, crying during micturition and poor urinary stream indicate an abnormality of the distal urinary tract. Diurnal incontinence, urgency, frequency and squatting suggest voiding dysfunction. Dysuria, frequent voiding and hypogastric pain suggest cystitis.

Fever, chills and rigors and flank pain indicate renal parenchymal involvement. Gross hematuria occasionally may be present. The presence of fever is regarded as indicative of pyelonephritis. Because of therapeutic implications it is useful to clinically differentiate between UTI involving renal parenchyma (pyelonephritis) from that confined to the bladder and urethra.

Patients with urinary stasis (mechanical or neurogenic) having UTI from urea-splitting organisms, usually *Proteus* but also *Klebsiella*, are at risk of developing hyperammonemia and encephalopathy.

### Recurrent Urinary Tract Infections

Some children usually girls in the school age group, with an anatomically and functionally normal urinary tract may develop recurrent lower tract, a febrile UTI. The risk of renal scarring in these patients is low. Some of these children may have symptoms of bladder instability, such as urge incontinence or squatting.

### Complicated Urinary Tract Infections

It implies the presence of either an anatomical abnormalities (e.g., obstruction, VUR,) or a functional abnormalities (e.g., neurogenic bladder, voiding dysfunction). These have symptoms that are consistent with pyelonephritis and have infections with more virulent organisms such as *Proteas*, *Pseudomonas* species.

### Pyelonephritis

Clinical pyelonephritis is characterized by any or all of the following: abdominal, back, or flank pain; fever; malaise; nausea; vomiting; and,

occasionally, diarrhea. Fever may be the only manifestation. Newborns can nonspecific symptoms such as poor feeding, irritability, jaundice and weight loss. Pyelonephritis is the most common serious bacterial infection in infants younger than 24 months of age who have fever without an obvious focus. These symptoms are an indication that there is bacterial involvement of the upper urinary tract involvement of the renal parenchyma is termed acute pyelonephritis, whereas if there is no parenchymal involvement, the condition is termed as pyelitis. Acute pyelonephritis can result in renal injury, termed pyelonephritic scarring.

Other findings vary, such as irritability, poor feeding, vomiting, decreased urinary output, and clinical evidence of dehydration. Infants with acute pyelonephritis usually have high fever without other localizing features; since their clinical presentation of UTI tends to be nonspecific.

## Cystitis

Cystitis is the most common clinical manifestation of infection of the urinary tract. Classic symptoms include urgency, frequency, or dysuria. Children may also have a history of difficulty in initiating the urinary stream. Occasionally, children may complain of abdominal or suprapubic pain. If fever is present, it is usually low grade. The urine may be foul smelling and cloudy.

Cystitis indicates that there is bladder involvement; symptoms include dysuria, urgency, frequency, suprapubic pain, incontinence, and malodorous urine. Cystitis does not cause fever and does not result in renal injury. Malodorous urine is not specific for a UTI.

Acute hemorrhagic cystitis often is caused by *E. coli*; it also has been attributed to adenovirus types 11 and 21. Adenovirus cystitis is more common in boys; it is self-limiting, with hematuria lasting approximately 4 days cystitis with hematuria. On imaging, typically there are multiple solid bladder masses that consist histologically of inflammatory infiltrates with eosinophils. Ureteral dilation with hydronephrosis also is common.

Interstitial cystitis is characterized by irritative voiding symptoms such as urgency, frequency, and dysuria, and bladder and pelvic pain relieved by voiding with a negative urine culture.

## Asymptomatic Bacteriuria

Asymptomatic bacteriuria refers to a condition in which there is a positive urine culture without any manifestations of infection. It is most common in girls.

### ESSENTIAL DIAGNOSTIC POINTS

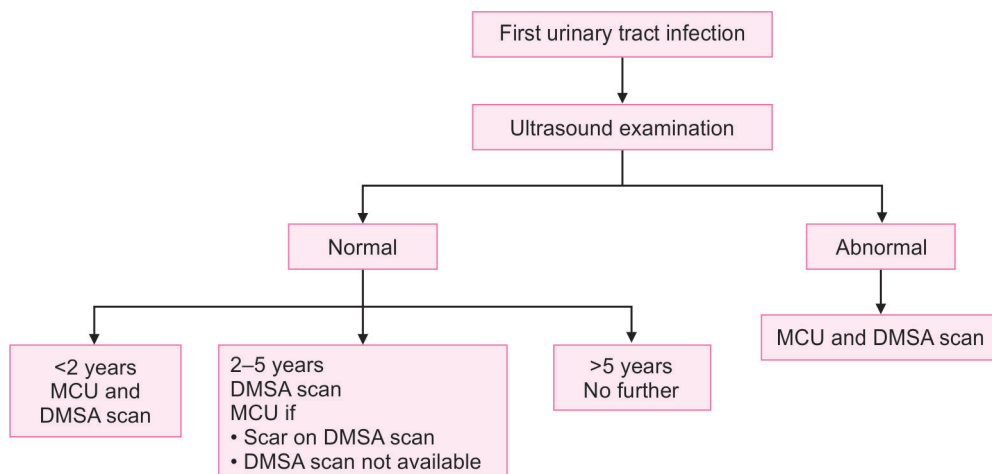
- Fever with rigors and chills
- Pain abdomen
- Vomiting
- Hematuria
- Pyuria
- Dehydration

## DIAGNOSIS (FLOWCHART 1)

### Urine Examination

The specimen should be transported to laboratory as early as possible. The urine is tested for protein and sugar, examined microscopically and cultured. There may be mild proteinuria in UTI.

**Flowchart 1:** Evaluation following initial UTI.



(MCU: micturating cystourethrogram; DMSA: dimercaptosuccinic acid)

Urine Microscopy

An uncentrifuged specimen is examined in a counting chamber. More than 10 WBC/cu mm are abnormal. The urine specimen may be centrifuged in standard manner (10 mL spun at the rate of 5000 rpm for 5 minutes, supernatant decanted off and sediment resuspended in the remaining 0.5 mL). Febrile UTI is usually associated with pyuria (>5 white cells/high power field in a centrifuged urine sample or more than 10 white cells/cu mm in uncentrifuged urine).

Detection of leukocytes (>5 WBC/HPF in centrifuged urine) and bacteria on microscopic examination of a carefully collected fresh sample of urine suggests UTI. Enhanced urinalysis using uncentrifuged urine sample for leukocyturia (>10 WBC/cu mm) in neubauer counting chamber along with Gram staining of sediment for bacteria is useful.

Nitrites and leukocyte esterase usually are positive in infected urine. Microscopic hematuria is common in acute cystitis, but microhematuria alone does not suggest UTI. White blood cell casts in the urinary sediment suggest renal involvement.

Sterile pyuria (positive leukocytes, negative culture) may occur in partially treated bacterial UTIs, viral infections, renal tuberculosis, renal abscess, UTI in the presence of urinary obstruction, urethritis as consequence of a sexually transmitted infection inflammation near the ureter or bladder (appendicitis, Crohn's disease), or interstitial nephritis (eosinophils).

Urine Culture

The criteria for the diagnosis of UTI depend on the method of collection of urine. On culture of urine collected by a standard midstream clean catch specimen, a colony count of more than 10<sup>5</sup> CFU/mL should be documented. A colony count below 10<sup>4</sup> is usually due to urinary contamination unless the child has polyuria or has received antimicrobial therapy. If urine sample is obtained by suprapubic aspiration (e.g., infants), any number of pathogens indicate UTI. On samples collected by urethral catheterization, a colony count of more than 5 × 10 CFU/mL, indicates UTI.

If the culture shows >50,000 colonies of a single pathogen (supra-pubic or catheter sample), or if there are 10,000 colonies and the child is symptomatic, the child is considered to have a UTI. In a bag sample, if the urinalysis result is positive, the patient is symptomatic, and there is a single organism cultured with a colony count >100,000, there is a presumed UTI. If any of these

criteria are not met, confirmation of infection with a catheterized sample is recommended.

Definitions of positive or negative cultures are dependent on the method of urine collection and the patient's clinical status. On culture, a colony count of more than 10<sup>5</sup>/mL organisms of a single species is considered confirmatory of UTI. Counts between 10<sup>4</sup> and 10<sup>5</sup>/mL may require reevaluation. Bacterial counts less than 10<sup>5</sup>/mL are significant if symptoms of UTI are present. The colony counts may be low if the urine is very dilute or antibiotic therapy has been started. Infants have a smaller bladder capacity and void frequently and therefore may have low colony counts.

The presence of even a few bacteria on a suprapubic specimen is abnormal (Table 1).

Dipstick Tests

Urinary bacteria convert nitrate to nitrite, which can be detected as a color change on chemically coated paper strips. The intensity of color change is proportional to the number of bacteria in the urine. Similarly production of esterase by neutrophils in the urine can be detected by chemical methods. Dipstick tests based on nitrite reduction and detection of leukocyte esterase correlate well with urine culture.

In a febrile infant or a child with symptoms suggestive of UTI, a urinalysis suspicious for UTI may include the presence of bacteria or WBCs on microscopy or the presence of leukocyte esterase (LE) or nitrites on dipstick. Nitrites result from the conversion of dietary nitrates to nitrites by gram-negative enteric bacteria such as *E. coli* and require about 4 hours in the bladder. A false-negative nitrite on a dipstick may be due to insufficient bladder time in young children who frequently empty their bladders in less than 4 hours or due to infection with bacteria that

TABLE 1: Diagnosis of urinary tract infection.		
Method of collection	Colony count (per mL)	Probability of infection
Suprapubic aspiration	Any number	99%
Urethral catheterization	>10 <sup>5</sup> 10 <sup>4</sup> –10 <sup>5</sup> 10 <sup>3</sup> –10 <sup>4</sup> <10 <sup>3</sup>	95% Very likely Suspicious; repeat Unlikely
Mid-stream void	>10 <sup>4</sup> >10 <sup>5</sup> 10 <sup>4</sup> –10 <sup>5</sup> <10 <sup>4</sup>	Very likely 90–95% Suspicious; repeat Unlikely

do not convert dietary nitrates to nitrites (e.g., *Enterococcus*, *Pseudomonas*, *Acinetobacter*, and *S. saprophyticus*). Leukocyte esterase is an enzyme found in WBCs and is a surrogate marker for WBCs in the urine. Leukocyte esterase has a specificity of about 78%; accordingly, false-positive results may be observed. The presence of bacteria on a Gram stain of a sample of fresh, uncentrifuged urine correlates with 10 CFUs/mL but requires more equipment and expertise than dipsticks.

## Blood Tests

With acute renal infection, leukocytosis, neutrophilia, and elevated serum erythrocyte sedimentation rate, procalcitonin, and C-reactive protein are common. However these are all nonspecific markers of inflammation, and their elevation does not prove that the child has acute pyelonephritis. With a renal abscess, the white blood cell count is markedly elevated to >20,000–25,000/cu mm. An elevated serum procalcitonin level is associated with pyelonephritis and a high risk of renal scarring. Because sepsis is common in pyelonephritis, particularly in infants and in any child with obstructive uropathy, blood cultures should be drawn before starting antibiotics if possible.

### LABORATORY SALIENT FINDINGS

- Pyuria
- Albuminuria
- Hematuria
- Leukocytosis
- Urine: Culture and sensitivity
- USG: Abdomen
- Radionuclide imaging

## Imaging Studies

In view of the high incidence of abnormalities of the kidney and urinary tract that are associated with UTI, it is essential that imaging studies be done. Earliest detection of VUR is particularly important since in the presence of severe VUR, UTI may lead to renal parenchymal scarring. Posterior urethral valves are commonly detected in male infants with UTI.

Structural abnormalities of the kidney and bladder dilatation can be detected on ultrasonographic evaluation, but a micturating cystourethrogram needs to be done to look for VUR and examine the distal urinary tract.

## Ultrasonography

It is an excellent, but observer dependent method. The anatomy of the kidney and urinary tract can

be satisfactorily examined. The interpretation of findings requires more expertise in neonates and infants.

## Intravenous Pyelography (IVP, Excretory Urogram)

This study provides sharper details and is a good indicator of kidney function. However, because of the hazards of radiocontrast agent and the high dose of radiation, the IVP is not performed provided a good ultrasonographic examination can be done.

## Micturating Cystourethrogram

A micturating cystourethrogram (MCU) is necessary to detect VUR and evaluate the distal urinary tract especially for posterior urethral valve. It also gives useful information on bladder dynamics as assessed by the filling and emptying of bladder and the amount of residual urine. Micturating cystourethrogram is done by introducing the radiocontrast medium into the bladder through a thin catheter, or directly through suprapubic puncture. The child's co-operation is necessary; an infant may be scared and unable to empty the bladder fully.

Micturating cystourethrogram is generally performed, with strict aseptic precautions, after the urine has been sterile for 3–4 weeks. Concern that obtaining an MCU too soon after a UTI may result in a false positive study for VUR is ill founded. Firstly, children who have VUR only when they have cystitis do have a significant problem, since reflux causes scarring by allowing bacteria to ascend. Secondly, it is rare for VUR to be detected during UTI and then to disappear following treatment.

Catheterization of the urinary tract, during MCU, carries the risk of introducing bacteria into the urinary tract. Antibiotic prophylaxis (oral cotrimoxazole in full dosage, first dose 12 hours before the procedure and three doses thereafter, or parenteral gentamicin 30 minutes before the procedure) reduces the risk of iatrogenic infections.

## Radionuclide Imaging

### INDICATIONS FOR IMAGING STUDIES

- Episode of acute pyelonephritis
- Boys with their first UTI
- Girls <3-year-old with their first UTI
- Girls >3-year-old with second UTI
- Family history of UTI-related features

*Dimercaptosuccinic acid (DMSA) scan:* It is superior to ultrasonography and IVP in detecting renal parenchymal scarring. It can also detect acute pyelonephritis, when decreased areas of tracer uptake are seen without distortion or normal renal outline.

*Direct radionuclide cystourethrogram (DRCG):* Instead of the radiocontrast agent, a radionuclide is introduced into the bladder. This procedure is more sensitive in detecting VUR, but the grading of VUR cannot be done. As it exposes the child to less radiation, it can be employed for follow-up studies.

TREATMENT

For febrile UTI the length of treatment should be 7–14 days. In an otherwise healthy child with suspected a febrile acute cystitis and without a history of recurrent UTI, a shorter course may be sufficient.

Oral and parenteral antibiotics are equally efficacious treatment for a UTI: The latter is indicated if the patient is either toxic or vomiting or if there are no oral options available (Tables 2 and 3).

Infection with *Enterococcus* is more common during early infancy; accordingly, antibiotic coverage for neonates should include intravenous ampicillin. Broader coverage should also be considered for patients with recent antibiotic exposure, recent hospitalization, or history of genitourinary anomaly because they are at risk for infection with a drug-resistant bacterial species. Increased coverage includes antipseudomonal penicillins, B-lactam/B-lactamase inhibitor combinations, fluoroquinolones, second-, third- or fourth-generation cephalosporins, and carbapenems. Fluoroquinolones are not a first-line consideration but are an effective choice when *Pseudomonas aeruginosa* is suspected or proven to be the cause of infection.

Infants below 3 months of age and children with complicated UTI should initially receive parenteral antibiotics. The risk of recurrent UTI is highest 3–6 months after the index infection. Parents should be educated regarding this possibility and encouraged to seek prompt treatment if a fever or symptomatic UTI develops again. Besides a recent UTI, risk factors for recurrent UTI include bladder and bowel dysfunction (voiding dysfunction and constipation) and congenital anomalies.

The urgency of treatment is particularly important in neonates and infants who should

TABLE 2: Empiric parenteral antibiotics.	
Agent	Dosages
Ceftriaxone	75 mg/kg/day
Cefotaxime	150 mg/kg/day, divided every 6–8 hours
Ceftazidime	100–150 mg/day, divided every 8 hours
Gentamicin	7.5 mg/kg/day, divided every 8 hours
Tobramycin	5 mg/kg/day, divided every 8 hours
Piperacillin	300 mg/kg/day, divided every 6–8 hours

TABLE 3: Empiric oral antibiotics.	
Agent	Dosages
Amoxicillin-clavulanate	20–40 mg/kg/day, divide in three doses
Trimethoprim-sulfamethoxazole	6–12 mg/kg trimethoprim and 30–60 mg/kg sulfamethoxazole/day divided in two doses
Sulfisoxazole	120–150 mg/kg/day, divided in one dose
Cefixime (third generation)	8 mg/kg/day
Cetpodoxime (third generation)	10 mg/kg/day, divided in two doses
Cefprozil (second generation)	30 mg/kg/day, divided in two doses
Cefuroxime (second generation)	20–30 mg/kg/day, divided in two doses
Cefalexin (first generation)	50–100 mg/kg/day, divided in four doses
Nitrofurantoin	5–7 mg/kg/day, divided in four doses

preferably be hospitalized to ensure supportive measures such as fluid therapy and control of pyrexia. Neonates and infants should receive parenteral antibiotics such as a combination of ampicillin and gentamicin, or cefotaxime or ceftriaxone.

Parenteral antibiotic therapy is also required, initially, in older children who have complicated UTI for the first 48–72 hours. Once the clinical condition improves and the oral intake is satisfactory, antibiotics may be given orally. Careful monitoring and repeated clinical examinations are required.

Children over 1 year, who are accepting feeds by mouth and are not toxic, may be treated with oral medications such as amoxicillin, cefaclor, cefalexin or cotrimoxazole have rendered them



less effective than others. Cefalexin has no activity against *P. vulgaris* and *Pseudomonas*. Norfloxacin and ciprofloxacin are broad-spectrum quinolones, which are active against *E. coli*,

*K. pneumoniae*, *P. mirabilis* and *Pseudomonas aeruginosa*. They should not be used as first-line agents and reserved for serious infections.

If treatment is initiated before the results of a culture and sensitivities are available, a 3- to 5-day course of therapy with trimethoprim-sulfamethoxazole (TMP-SMX) or trimethoprim is effective against many strains of *E. coli*. Nitrofurantoin (5–7 mg/kg/24 h in 3–4 divided doses) also is effective and has the advantage of being active against *Klebsiella* and *Enterobacter* organisms. Amoxicillin (50 mg/kg/24 h) also is effective as initial treatment but has a high rate of bacterial resistance.

Acute cystitis should be treated promptly to prevent possible progression to pyelonephritis. If the symptoms are severe, presumptive treatment is started pending results of the culture. If the symptoms are mild or the diagnosis is doubtful, treatment can be delayed until the results of culture are known, and the culture can be repeated if the results are uncertain.

In acute febrile infections suggesting clinical pyelonephritis 7–14 days course of broad-spectrum antibiotics capable of reaching significant tissue levels is preferable. Children who are dehydrated, are vomiting, are unable to drink fluids, are 1 month of age or younger, have complicated infection, or in whom urosepsis is a possibility should be admitted to the hospital for IV rehydration and IV antibiotic therapy.

Initial oral antibiotic options include cephalosporins, amoxicillin-clavulanate, or trimethoprim-sulfamethoxazole. Sulfonamides should be avoided in premature infants or newborns younger than 4 weeks given the risk of hyperbilirubinemia, jaundice, and kernicterus. Nitrofurantoin does not reach adequate concentrations in tissue, so it is not a good option if Pyelonephritis is suspected. Nitrofurantoin should also be avoided in neonates and those with renal insufficiency, liver dysfunction, and glucose-6-phosphate dehydrogenase deficiency.

Parenteral treatment with ceftriaxone (50–75 mg/kg/24 h, not to exceed 2 g) or cefotaxime (100 mg/kg/24 h), or ampicillin (100 mg/kg/24 h) with an aminoglycoside such as gentamicin (3–5 mg/kg/24 h in 1–3 divided doses) is preferable. The potential ototoxicity and nephrotoxicity of aminoglycosides should be considered; serum

creatinine should be obtained before initiating treatment, and daily trough gentamicin levels should be obtained during therapy. Treatment with aminoglycosides is particularly effective against *Pseudomonas* sp., and alkalinization of urine with sodium bicarbonate increases its effectiveness in the urinary tract.

Oral third-generation cephalosporins such as cefixime are as effective as parenteral ceftriaxone against a variety of gram-negative organisms other than *Pseudomonas*, and these medications are considered by some authorities to be the treatment of choice for oral outpatient therapy.

The oral fluoroquinolone ciprofloxacin is an alternative agent for resistant microorganisms, particularly *Pseudomonas*, in patients older than age 17 years. It also has been used on occasion for short-course therapy in younger children with *Pseudomonas* UTI. Levofloxacin is an alternative quinolone with a good safety profile in children. However, the clinical use of fluoroquinolones in children should be used with caution because of potential cartilage damage. In some children with a febrile UTI, intramuscular injection of a loading dose of ceftriaxone followed by oral therapy with a third-generation cephalosporin is effective. A urine culture 1 week after the termination of treatment of a UTI ensures that the urine is sterile but is not routinely needed. A urine culture during treatment almost invariably is negative.

In a child with recurrent UTIs, identification of predisposing factors is beneficial. Antimicrobial prophylaxis using trimethoprim or nitrofurantoin once a day is another approach to this problem. It is unnecessary in most children with recurrent UTIs in the absence of severe reflux. Prophylaxis with TMP-SMZ, amoxycillin, or cefalexin can also be effective, but the risk of breakthrough UTI may be higher because bacterial resistance may be induced.

## Response to Treatment

With appropriate treatment the urine becomes sterile after 24 hours and microscopic examination of urine does not show bacteriuria, although neutrophils may persist for a few days. Within 2–3 days the symptoms disappear. Failure to respond to therapy suggests (i) nonsensitivity of the pathogens, (ii) Presence of complicating factors, or (iii) noncompliance. If the expected clinical response does not occur with two days of antimicrobial therapy, another urine specimen should be cultured and an ultrasonography performed to exclude complicating factors.

Preventing Recurrent UTI (Table 4)

Prophylactic antibiotics are administered to young infants. The medication is given as single bedtime dose. Long-term antibiotic prophylaxis is recommended in patients with VUR and in those with frequent febrile UTI (three or more episodes in a year), even if the urinary tract is normal. Circumcision reduces the risk of recurrent UTI in infant boys and might have benefits in patients with high grade VUR.

TABLE 4: Antibiotics for prophylaxis.		
Drug	Dosage (mg/kg/day)	Remarks
Cotrimaxazole	1–2 of trimethoprim	Maintain adequate fluid intake; avoid in infants <6 weeks age and G6PD deficiency
Nitrofurantoin (NFT)	1–2	Considerable GI upset; contraindicated in G6PD deficiency, infants <3 months and renal insufficiency; efficacy reduced with decreasing renal function; does not interfere with intestinal flora; bacterial resistance is rare
Cefalexin	10–12	Use in young infants where use of NFT and cotrimoxazole is restricted

GENERAL MEASURES AND SURVEILLANCE

INDICATIONS FOR PROPHYLACTIC ANTIBIOTICS

- Infants or children on treatment and waiting for laboratory reports.
- Children with known urological abnormalities.
- Adolescent with recurrent UTI.

ANTIBIOTICS FOR PROPHYLAXIS

- Trimethoprim/sulfamethoxazole
- Nitrofurantion
- Sulfisoxazole
- Nalidixic acid
- Methenamine mandelate

RISK FACTORS FOR PERMANENT RENAL DAMAGE

- Younger age
- Obstruction
- VUR
- Recurrent infections
- Pyelonephritis
- Nephrolithiosis
- Delay in diagnosis and initiation of therapy

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# Acute Hemiplegia of Childhood

## PRESENTING COMPLAINTS

A 4-year-old girl was brought with the complaints of:

- Fever since 3 days
- Vomiting since 2 days
- Abnormal movements of left upper limb and lower limb since 1 day
- Not able to move on left side of the body since morning.

## History of Presenting Complaints

A 4-year-old girl was brought by mother with the history of not able to move the left upper limb and lower limb since she got up in the morning. Mother has noticed the complete weakness on the left side. Mother gave the history of tonic-clonic convulsions on the left side in the previous evening. For the same she showed the daughter

to her family doctor. There were about 2–3 such attacks each lasting 5–8 minutes in the night. As mother noticed that her daughter was not able to move the left side of the limbs, she rushed to the hospital.

Mother also gave the history of fever since 3 days. Fever was of moderate to high degree, intermittent which used to get relieved by paracetamol. There was history of vomiting since previous day. The child had projectile type of vomiting. Child had vomited about 3–4 times.

## Past History of the Patient

She was the only sibling of the nonconsanguineous marriage. She was born at full term by vaginal delivery. Her birth weight was 3 kg. She started taking breast milk immediately after the birth. There was no significant postnatal event. Weaning was started at 4th month and completed by 1 year. She was immunized completely. All the developmental milestones were normal.

## CASE AT A GLANCE

### Basic Findings

Height	: 97 cm (75th centile)
Weight	: 14 kg (50th centile)
Temperature	: 39°C
Pulse rate	: 126 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 70/50 mm Hg

### Positive Findings

#### History

- Convulsion
- Fever
- Vomiting
- Weakness in left limb

#### Examination

- Moderate dehydration
- Altered sensorium
- Left upper and lower limb hypotonia
- DTR absent
- Signs of meningitis

#### Investigation

- TLC: Raised
- CSF: Turbid, polymorphs cell present

## EXAMINATION

The girl was moderately built and nourished. There were finding of moderate dehydration. The anthropometric measurements included the height was 97 cm (75th centile) and weight was 14 kg (50th centile).

The child was febrile (39°C). The pulse rate was 126 per minute and respiratory rate was 26 per minute. The blood pressure recorded was 70/50 mm Hg. There was no pallor, no lymphadenopathy, cyanosis and clubbing.

There was altered sensorium, but was responding to the oral command sluggishly. She was responding to painful stimulus by resisting the stimulus. There was complete flabbiness on the left upper and lower limbs. She was not at all moving to the painful stimulus. Deep tendon reflexes were absent. Neck rigidity and Kernig's sign were present. There were signs of meningitis. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 14,600 cells/cu mm
DLL	: $P_{68} L_{28} E_2 M_2$
ESR	: 36 mm in the 1st hour
Platelet count	: 1.6 lac/cu mm
X-ray chest	: Normal
Mantoux test	: Negative
CSF examination	: Turbid, elevated cell count mainly poly morphs. Sugar was 20 mg/dL. Gram stain-negative
CT scan	: Inflammatory changes preset
EEG	: Normal
MR angiogram	: Normal

## DISCUSSION

It is often due to the cerebrovascular disorders. There will be often history of ear, throat, mastoid infection. This is associated with cardiac disease or hematological disorders. This will help to determine the cause of the acute hemiplegia.

Ischemic and hemorrhagic strokes result in the loss of neurologic function of the corresponding injured regions of the brain. It is a common cause of neonatal seizures and cerebral palsy, and stroke often leads to permanent cognitive and motor deficits. Stroke is often under recognized in children, particularly during the acute period. Prompt recognition and treatment may potentially reduce morbidity and mortality rates.

The incidence of stroke in childhood ranges from 2 to 13 per 100,000 children per year. For unclear reasons, childhood arterial ischemic stroke is more common in boys than girls. In neonates, the occurrence of stroke is greater than that of childhood stroke and occurs in approximately 1 in 4000 births. Neonatal nontraumatic hemorrhagic stroke has an estimated incidence of 1.1 per 1000 live births.

Stroke is classified broadly into two types: ischemic and hemorrhagic stroke. Ischemic stroke occurs when a thrombotic or embolic occlusion creates loss of perfusion to an area of the central nervous system. Bleeding occurring into brain parenchyma is classified as hemorrhagic stroke. Ischemic stroke occurs more commonly than does hemorrhagic stroke.

In pediatric patients, strokes are additionally classified based on age. Perinatal strokes, sometimes referred to as neonatal strokes, occur in

infants up to 28 days of age. In older infants and children up to age 18 years, this disease is referred to as childhood stroke. This distinction is important because risk factors, treatments, and outcomes are different in these two groups of pediatric patients.

## CAUSES

1. Cerebrovascular occlusive disease
  - a. Venous thrombosis of sinus
  - b. Arterial thrombosis
  - c. Cerebral embolism
2. Intracranial hemorrhage
  - a. AV malformation
  - b. Hypertension
  - c. Struge-Weber syndrome
  - d. Trauma
3. Inflammatory granuloma
4. Cerebral abscess
5. Meningitis
6. Intracranial space occupying lesion

## RISK FACTORS

Many risk factors are associated with childhood stroke. The most common risk factors for arterial ischemic, stroke in childhood are cardiac disease (congenital or acquired), hemoglobinopathies such as sickle cell disease, and arterial dissection. Other risk factors include prothrombotic states, infection, autoimmune diseases, drug use, trauma, and radiation exposure. A risk factor for stroke is identifiable in the majority of children with stroke.

Heart disease, both congenital and acquired, is the most common risk factor identified in patients with childhood strokes. The highest risk time for stroke seems to be during periprocedural or perioperative time frames. The role in childhood stroke of common cardiac abnormalities such as patent foramen ovale and mitral valve prolapsed is unknown, but complex cardiac conditions that greatly alter hemodynamics carry an increased risk of thrombus formation.

Infectious diseases that have been associated with ischemic and hemorrhagic stroke include meningitis, tonsillitis, otitis media, and viral infections such as varicella infection may cause areas of focal vascular narrowing or may cause an inflammatory vasculitis leading to stroke. The incidence of stroke related to infection has decreased dramatically with improvements in vaccination strategies and antimicrobial therapy.

Numerous types of vasculopathies are associated with childhood stroke and include dissection, moyamoya vasculopathy, postviral arteriopathy,

radiation-induced arteriopathy, vasculitis, and fibromuscular dysplasia. There are genetic risk factors for some vasculopathies.

Hypercoagulable states, many of which are inherited thrombophilias, are often seen associated with stroke in the young. They include antithrombin deficiency, protein C deficiency, protein S deficiency prothrombin gene mutations, anticardiolipin antibodies, and lupus anticoagulant.

Sickle cell disease, specifically hemoglobin SS disease (sickle cell anemia) and sickle-B-thalassemia, is one of the most common causes of stroke in the pediatric population. The highest risk population has the genotype hemoglobin SS. Sickle cell disease is considered a hypercoagulable state. The risk of hemorrhagic stroke in this population increases with age, with more frequent presentation in late adolescence and early adulthood. Children with sickle cell disease have an increased risk of aneurysm development, and often aneurysms are multiple when they develop. As a strategy for preventing primary stroke, children with sickle cell disease are screened for stroke risk using transcranial Doppler ultrasound to identify early signs of vascular narrowing. Elevated transcranial Doppler velocities of greater than or equal to 200 cm/s are associated with increased risk of stroke. Consultation with a hematologist is essential in this situation, as these children may be started on chronic transfusion therapy for primary stroke prevention.

### CLINICAL FEATURES (FIG.1)

Childhood stroke is defined as stroke occurring after 28 days of age until age 18 years. Approximately 55% are reported to be ischemic, and the remaining 45% are hemorrhagic strokes.

The mode of onset varies with the cause. Children with stroke present similarly to adults. Focal motor symptoms such as monoparesis, hemiparesis, or, rarely, quadriplegia may result. Focal sensory loss can occur. Vision loss affecting or both eyes may occur and may manifest as visual field defects. Slurred speech, or dysarthria, is a common symptom reflecting motor impairment of speech production. Aphasia, which is loss of expressive or receptive language fluency, is seen typically in infarcts of the dominant hemisphere or, rarely, in regions of the thalamus.

Maximum neurological signs with the sudden onset will be associated with emboli. Seizures are frequently associated. Head and neck rigidity will be associated with intracranial hemorrhage and

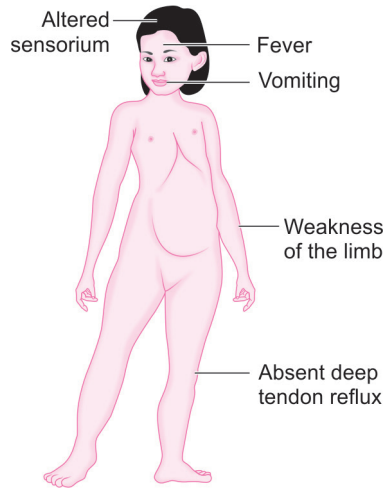


Fig. 1: Clinical features.

infection. The relatively late onset is seen with cerebrovascular thrombosis.

There is circumduction of the walking. The movements of the upper extremities are asymmetric. There will be lateral propping reaction. This is the protective reaction by the child from falling, i.e., extension of the arm. This happens when the child is pushed from sitting position.

This reaction is asymmetric in spastic hemiplegia. Absence of the propping reaction in infants after the age of 8–9 months is always abnormal. Multifocal seizures, raised intracranial pressure and vomiting are common features of superior sagittal sinus thrombosis.

Arterial occlusions are associated with hemiparesis and seizures. These generally occur within 2 years. These seizures are very difficult to control with medication. Hemiparesis, cerebral hemihypertrophy and cerebral porencephaly may result.

Specific pattern of motor deficit is seen with cortical lesions. This depends upon the vascular distribution of the artery. Seizures and cortical necrosis are usual. Aphasia is common or dominant in left sided lesion. Lack of attention for objects is seen with parietal lesions.

Other symptoms include motor in coordination, gait ataxia, diplopia, vertigo, and, rarely, altered levels of consciousness. Although these, symptoms can occur in isolation, they more typically occur in combination. Some patients may experience weakness of the palatal musculature and develop dysphagia, or poor ability to swallow. Seizures occur more commonly with stroke in childhood than with stroke in adulthood, particularly in children younger than the age of 1 year.



Although symptoms such as change in levels of consciousness are more commonly seen in hemorrhagic rather than ischemic stroke, there are no specific symptoms that can distinguish ischemic from hemorrhagic strokes.

Stroke-like symptoms can be seen in other conditions such as acute demyelinating disease, tumor, Todd paralysis, and hemiplegic migraine. However, a study evaluating the presence of stroke mimics when children present to the hospital with stroke symptoms found that stroke mimics were present only 20% of the time numerous studies have shown a delay in diagnosing stroke in childhood. Prompt recognition of this disease is necessary because of the emergent need to potentially stabilize the patient.

#### GENERAL FEATURES

- Altered sensorium
- Nausea and vomiting
- Headache
- Signs of meningitis
- Spasticity
- Seizures
- Aphasia

#### ESSENTIAL DIAGNOSTIC POINTS

- Sudden in onset
- Seizures
- Raised intracranial pressure
- *Gait disturbances*: Circumduction
- Aphasia
- Cerebral hemihypertrophy
- Cerebral porencephaly

### LOCALIZATION

Cortical lesions are characterized by the specific pattern of motor deficit, depending on the vascular distribution of the artery involved. Seizures and cortical sensory loss are usual.

In the left-sided lesion, aphasia is a dominant clinical feature. The child finds difficulty in reading, writing and comprehension. Organization of space and body image are affected. In right parietal lesions, the child exhibits lack of attention for objects on his left side. He may ignore the left side of a picture placed before him or may not even recognize his left hand. He has difficulty in copying simple figures, (indicating constructional apraxia). He gets lost easily and confuses directions given to him because of spatial disorganization.

Corona radiata lesions produces the hemiplegia is generally complete and seizures are absent. With internal capsule affection, hemiplegia is complete, often with sensory loss.

Midbrain involvement includes hemiplegia affects the contralateral side and paralysis of 3rd and 4th cranial nerves of the same side (Weber syndrome).

Hemiplegia affects the opposite side and involves paralytic of 6th and 7th cranial nerves on the same side (Millard-Gubler syndrome) with the affection of the pons.

Contralateral hemiplegia with ipsilateral involvement of lower cranial nerves is noted in the involvement of medulla oblongata.

### DIAGNOSIS

The evaluation requires accurate history, thorough clinical examination, investigations and neuroimaging. A patient presenting with stroke should be investigated in a systematic fashion. All patients coming with acute onset neurological deficit should first undergo neuroimaging. Magnetic resonance imaging (MRI) is the investigation of choice since computed tomography (CT) cannot pick up an infarct in early stage. In case MRI cannot be done a plain CT scan is mandatory. This will help to differentiate between infarction and hemorrhage and rule out other diagnosis.

Magnetic resonance imaging is a valuable tool for evaluation of stroke and should be used as a first-line investigation, but it is more expensive, less readily available and more time consuming. Diffusion weighted MRI is even more sensitive than conventional MRI. The other advantage of MRI is that magnetic resonance angiography (MRA) and MR venography can be done at the same time if necessary. This helps to elucidate noninvasively the vascular anatomy of cerebral vessels and demonstrates stenosis or occlusion in ischemia and vascular malformation in cases with hemorrhage. Hence, it helps to obviate the need for invasive cerebral angiography in majority of patients. Imaging of the cervical and proximal intracranial arterial vasculature should be performed in all children with arterial ischemic stroke.

The diagnostic evaluation in a patient with stroke is aimed at confirming the diagnosis of cerebrovascular disease, define extent, type of stroke (ischemic or hemorrhagic), and to determine the vascular territory (large vessel versus small vessel) and, if possible, to identify the underlying etiology of stroke.

The stroke like picture can be seen in variety of conditions and the diagnosis of cerebrovascular disease has to be confirmed by neuroimaging. The causes of stroke in children are varied and it is important to identify the underlying cause

as it has implications on the management, future recurrences, prognosis and even genetic counseling of the family.

After confirming the existence of infarct or hemorrhage, one should investigate further to determine the etiology of stroke. All patients should have a thorough cardiac examination, chest X-ray, electrocardiogram and echocardiogram as underlying heart disease is a very common cause of stroke in the pediatric population. If transthoracic echocardiography is noncontributory and the suspicion of cardiac source of embolism is high, then the patient should be subjected to transesophageal echocardiography.

Cerebrospinal fluid analysis is mandatory in a stroke patient with unexplained fever or signs of central nervous infections.

#### LABORATORY SALIENT FINDINGS

- Evaluation of predisposing illness
- MCV; MCH; serum iron
- CSF lactate and pyruvate
- Chest X-ray and ECG
- Neurological workup
- CT scan, EEG, and MR angiography
- Lumbar puncture

## TREATMENT

Any patient, regardless of age, presenting with symptoms of stroke requires emergent medical evaluation. Initial management, as with any patient with a medical emergency, includes assessment and stabilization of airway, breathing, and circulation. Continuous cardiac and pulse oximetry monitoring should be instituted, and oxygen should be administered when necessary.

A detailed neurologic examination should be performed. Laboratory studies ordered during the assessment of a child with stroke may include complete blood count, prothrombin time, partial thromboplastin time, fibrinogen, blood glucose; electrolyte panels, type and screen, hemoglobin profile, and markers for thrombophilia.

Neuroimaging is essential to distinguish between hemorrhagic and ischemic stroke and to differentiate between stroke and stroke mimics CT of the brain is performed in the emergency setting to evaluate for signs of hemorrhage. Ischemic stroke may not always be apparent on CT of the brain, particularly if the CT is obtained early in the clinical course. MRI of the brain is used to differentiate between stroke and other causes of focal neurologic deficits.

Magnetic resonance angiography of the head and neck is often used as a noninvasive method

to evaluate for arterial abnormalities. Magnetic resonance venography (MRV) of the head is used with ischemic or hemorrhagic infarcts that are not localized to typical arterial distributions. CT angiography and venography are alternative imaging modalities that may be used for children who are unable to undergo MRI.

Ischemic or hemorrhagic stroke causing hydrocephalus or severe mass effect may require neurosurgical intervention for decompression. Hemicraniectomy and other decompressive surgical techniques are used frequently in the acute and subacute ischemic stroke period in adults presenting with signs and symptoms of severe mass effect due to their ischemic stroke, typically because of large territory infarctions of the middle cerebral artery or cerebellar infarctions. Early neurosurgical consultation for hemorrhagic infarctions and for ischemic lesions associated with significant mass effect is recommended.

## Treatment of Hemorrhagic Stroke

Because of the risk of rapid deterioration in patients with hemorrhagic stroke, rapid diagnosis and stabilization are crucial. Focal or generalized seizures have been reported and these children may benefit from prophylactic antiepileptic medications. Investigations for the etiology of hemorrhage, such as arterial venous malformations (AVMs), intracranial aneurysms, or hemophilia, are warranted. AVMs and intracranial aneurysms may require conventional angiography, to diagnose and may necessitate neurosurgical treatments or treatments by interventional radiology. Factor replacement therapy for hemophilias is useful to prevent future hemorrhage in this population, and long-term management with a hematologist is necessary.

## Treatment and Prevention of Ischemic Stroke

Treatment of ischemic stroke is classified as either primary or secondary stroke prevention. The goal of primary stroke prevention is to prevent a first stroke occurrence. Secondary stroke prevention is targeted at preventing stroke recurrence.

For the primary stroke prevention children with sickle cell disease should be screened from approximately age 2 with transcranial Doppler ultrasound looking for evidence of intracranial stenosis. Elevated Doppler velocities of greater than or equal to 200 cm/s indicate an increased risk of having a stroke. Studies in this population have shown that they may benefit from chronic

transfusion therapy. Growing evidence indicates the use of hydroxyurea as a potential agent for primary stroke prevention in children with elevated Doppler velocities.

For the secondary stroke prevention, few data in pediatrics are available. The choice of antithrombotic therapy used for prevention the etiology of infarction. Aspirin therapy is used frequently to prevent recurrent stroke, unless there are complicated cardiac or prothrombotic disorders associated with ischemic stroke. In the setting of complex cardiac or prothrombotic risk factors that carry a high risk of stroke recurrence, anticoagulation with warfarin or low molecular-weight heparin is often recommended. Collaboration with hematology experts is often used in this setting.

In the management of acute ischemic stroke in adults, intravenous tissue plasminogen antigen and intra-arterial therapies with thrombolytic medications' and mechanical clot-retrievers are used emergently within the first few hours of the onset of stroke symptoms to recanalize the thrombosed artery, restore perfusion, and prevent or limit permanent ischemic damage. In adult ischemic stroke, these therapies have been shown to reduce morbidity and mortality rates; they do, however, carry a risk of intracerebral hemorrhage.

## PROGNOSIS

It is worse below 3 years of age especially with respect to seizures and mental retardation. There will be atrophy of hemiplegic side and post-hemiplegic athetosis may be seen.

Cerebral hemiatrophy with the flattening of the skull and pencephaly secondary to parenchymal damage may occur.

## Outcome of Childhood Stroke

Complex cardiac disease, vasculopathy, and specific prothrombotic risk factors such as elevated lipoprotein and protein deficiencies have been associated with risk of recurrence. Patients with hemorrhagic stroke have a higher risk of mortality compared with patients with ischemic stroke. Permanent neurologic deficits are common, most commonly hemiparesis and neuropsychological deficits and are reported in between 40 and 80% of childhood stroke survivors.

## CONCLUSION

Perinatal and childhood strokes, although rare diseases, are life-threatening and disabling conditions; leading to a potentially long lifetime of disability in the survivors. Much of what is known in stroke in the pediatric population is gathered from small cohorts of patients. At this time, because of the paucity of data, the guidelines for treatment are often based on research findings in adult stroke. It is essential to identify stroke promptly in this population to reduce morbidity and mortality rate. Further research in the management of stroke in infants and children is vital.

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# Cerebral Palsy

## PRESENTING COMPLAINTS

An 18-month-old boy was brought with the complaints of:

- Abnormal walking since 15 days
- Not swinging the hands during walking since 15 days
- Delayed developmental milestone since birth

## History of Presenting Complaints

An 18-month-old boy was brought to hospital with history of abnormal gait. Mother had noticed this as her child had started walking about 15 days back. Mother had also told that all other motor developmental milestones were delayed. She had also noticed the difference of the stance of the left upper limb. The left arm was abducted at the shoulder and flexed at the elbow. The left hand was not swinging during walking.

## Past History of the Patient

The boy was the first sibling of consanguineous marriage. The boy was born at full term.

Fetal condition was normal in the latent and early phase of the labor. Fetal distress was noted in later part of delivery. Hence the baby was extracted by emergency lower segment cesarean section (LSCS). Apgar score at one minute was 6/10. Child had to be intubated and needed resuscitation to establish spontaneous respiration. This took around 10 minutes. Apart from this child became normal and recovered with no other postnatal events. The birth weight was 2.6 kg. The child was discharged after 10 days. He was taking breastfeeds at the time of discharge. He was breastfeed exclusively till the age of 4 months and gradually brought to the family food at the age of 15 months. During this time he never had any major health problem. All the developmental milestones were delayed. He started walking without support at the age of 17 months. Then his mother noticed the abnormal gait and brought to the hospital. The child had been immunized completely.

## EXAMINATION

The boy was moderately built and nourished. He was alert and playing with toys on the examination table. He was not moving his left hand properly while playing. His anthropometric measurements included, his height 82 cm (90th centile), his weight 11 kg (80th centile), the head circumference was 47 cm. Anterior fontanelle was open and tense. He was afebrile, the pulse rate was 110 per minute, the respiratory rate was 18 per minute. Blood pressure recorded was 60/40 mm Hg. There was no pallor, no icterus, no lymphadenopathy, and no edema.

Left arm was abducted at the shoulder and flexed at the elbow. It was swinging during walking, movement on left side was less. These were suggestive of spastic hemiplegic gait. Vision and hearing was normal. There was no cranial nerve involvement and no sensory deficits. All other systemic examinations were normal.

### CASE AT A GLANCE

#### Basic Findings

Height	: 82 cm (90th centile)
Weight	: 11 kg (80th centile)
Temperature	: 37°C
Pulse rate	: 110 per minute
Respiratory rate	: 18 per minute
Blood pressure	: 60/40 mm Hg

#### Positive Findings

##### History

- Abnormal gait
- Fetal distress
- Asphyxia
- Delayed motor milestones

##### Examination

- Spasticity
- Abnormal gait
- Delayed milestones

##### Investigation

- NAD

INVESTIGATION

Hemoglobin	: 10 g/dL
TLC	: 8,900 cells/cu mm
Platelet count	: 3,00,000 cells/cu mm
X-ray chest	: Normal
X-ray skull	: Normal
ECG	: Normal
EEG	: No significant finding
CT scan brain	: Normal

DISCUSSION

Cerebral palsy (CP) is a persistent disorder of movement and posture, as a result of non-progressive disorder of immature brain. Cerebral palsy is unique as it involves static lesion upon which maturation and development are superimposed. Its manifestations depend on the stage of development and thus may appear to change over time. It is frequently accompanied by epilepsy, sensory impairment and mental retardation.

Infants with very low birth weight have a significant increase in the risk of cerebral palsy compared to normal birth weight children. Very premature infants (<28 weeks) are also much more likely to have cerebral palsy than term infants, which is thought to be related to the immature germinal matrix leading to increased risk of ischemic or hemorrhagic injury.

The motor disorders are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior as well as by epilepsy and secondary musculoskeletal problems. Cerebral palsy is caused by a broad group of developmental, genetic, metabolic, ischemic, infectious, and other acquired etiologies that produce a common group of neurologic phenotypes. Cerebral palsy has historically been considered as static encephalopathy, but some of the neurologic features of CP, such as movement disorders and orthopedic complications, including scoliosis and hip dislocation, can change or progress over time. Many children and adults with CP function at a high educational and vocational level, without any sign of cognitive dysfunction.

RISK FACTORS

Prematurity

Risk factors for cerebral palsy (Table 1) in preterm infants include premature rupture of membranes, chorioamnionitis, monochorionic twin placenta-tion and respiratory distress syndrome, broncho-pulmonary dysplasia and abnormal findings on

TABLE 1: Risk factors for cerebral palsy.

Prenatal	Perinatal	Postnatal
<ul style="list-style-type: none"><li>• Infections—TORCH</li><li>• Fetal anoxia</li><li>• Maternal diabetes</li><li>• Hypertension</li><li>• Maldevelop-ment of brain</li></ul>	<ul style="list-style-type: none"><li>• Asphyxia</li><li>• Prematurity</li><li>• APH</li><li>• Drugs</li><li>• Birth trauma</li></ul>	<ul style="list-style-type: none"><li>• CNS infections</li><li>• Trauma</li><li>• Toxins, e.g., lead</li><li>• Anoxia due to cardiac arrest, drowning</li><li>• Intracranial bleed</li></ul>

cranial ultrasound—periventricular leukomalacia (PVL) and ventriculomegaly.

Asphyxia

Preterm infants a strong relationship between spastic diplegia and hypoxic-ischemic encephalopathy (HIE) induced periventricular leukomalacia has been demonstrated. The association of hypoxia and cerebral palsy in term infants is much harder to substantiate.

Infections

Intrauterine viral infections—rubella herpes simplex and cytomegalovirus cause CNS injury. It will be manifest as cerebral palsy with spastic quadriplegia as the most common type. Approximately 10% of infants infected with cytomegalovirus will manifest with cerebral palsy.

Prenatal Abnormalities

Maternal disorders which can interfere with normal fetal nutrition oxygenation such as placental infarction, intrauterine infections, congenital malformations of the brain including neuronal migration defects and cerebral dysgenesis can manifest as cerebral palsy. Facial dysmorphism and presence of minor malformations point to prenatal origin of cerebral palsy.

Biochemical Abnormalities

Kernicterus is a classic example of biochemical abnormality causing cerebral palsy. Besides Rh incompatibility, bilirubin encephalopathy can occur in low birth weight children with additional risk factors, e.g., sepsis. Cerebral palsy following kernicterus has distinct clinical features—choreoathetosis, sensorineural hearing loss, enamel dysplasia and upward gaze palsy.

Postnatal Causes

Viral and bacterial infections of central nervous system are major risk factors. Gastroenteritis with



hypernatremic dehydration and accidental injuries are other common causes of cerebral palsy.

Perinatal problems such as prolonged difficult delivery, antepartum hemorrhage are observed in a significant proportion of children with tetraplegia. Intrauterine infections and congenital malformations of brain are also associated with this type of cerebral palsy.

#### ESSENTIAL DIAGNOSTIC POINTS

- Chronic static impairment of muscle tone
- Nonprogressive neuromuscular disorder
  - Hyperreflexia
  - Microcephaly
  - Ataxia
  - Involuntary movements

## CLASSIFICATION

#### CLASSIFICATION OF CEREBRAL PALSY

##### Tone and topography:

- *Spasticity*: Quadriplegia, diplegia, hemiplegia
- *Dyskinetic*: Choreoathetosis, dystonic
- Ataxic
- Mixed
- Hypotonic

##### Severity:

- *Mild*: Physical findings but no limitation in ordinary activities
- *Moderate*: Definite difficulty in daily activity and need for assistive devices
- *Severe*: Moderate to great limitation in everyday activity

## PATHOLOGY

Pathological changes include cerebral atrophy, porencephaly and degeneration of basal ganglia. Gliosis or contralateral hemiparesis results from vascular occlusion.

## CLINICAL FEATURES (FIG. 1)

### Clinical Types and Manifestations

Cerebral palsy is difficult to diagnose during the 1st year of life because:

- Hypotonia is more common than hypertonia and spasticity.
- Early abundance of primitive reflexes may confuse clinical picture.
- Limited variety of volitional movements for evaluation.

### Spastic Cerebral Palsy

The most common form is spastic cerebral palsy. This comprises about 65% of the cerebral palsy patients. This is due to the involvement of motor

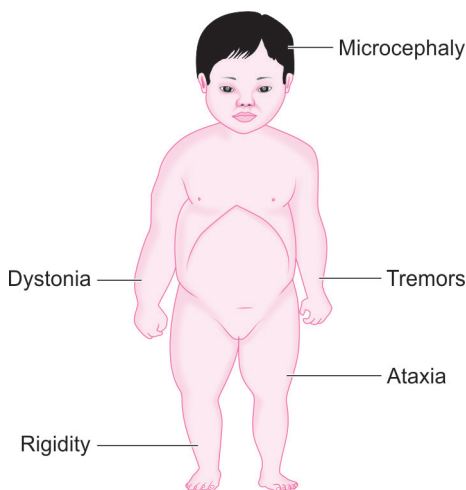


Fig. 1: Clinical features.

cortex and pyramidal system. They may have spastic quadriplegia, diplegia and hemiparesis. Early features include abnormally persistence of neonatal reflexes.

They are often hyperexcitable and have a firm grasp reflex. Spasm of adductor muscles manifests as scissoring of the lower limbs. The stretch reflexes are brisk. They may suffer from pseudobulbar palsy and some may be ataxic.

In neonatal period, hypotonia, lethargy and feeding difficulties are the cause of concern. Therefore baby looks almost normal for 2–3 months although there is delay in motor milestones. Gradually hypotonia disappears and child shows generalized increase in tone. The evaluation varies but reaches the spastic stage by the age of 2–3 years. Upper limbs are less affected as compared to lower limbs. Hence, locomotion is more impaired compared to manipulation (Figs. 2 to 4).

Spasticity is characterized by increased muscle tone, stereotyped and limited patterns of movements, decreased active and passive range of movements, the tendency to develop contractures and deformities, the persistence of primitive and tonic reflexes and poor development of postural reflex mechanism.

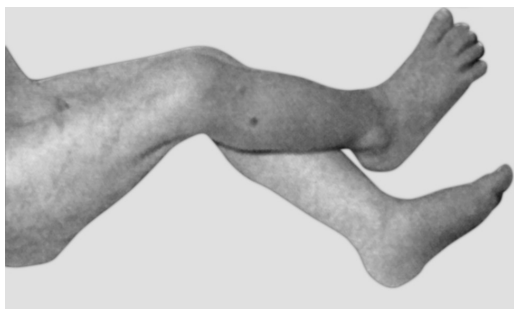
Spasticity refers to the quality of increased muscle tone, which increases with the speed of passive muscle stretching and is greatest in antigravity muscles. It is apparent in the affected extremities, particularly at the ankle, causing an equinovarus deformity of the foot. An affected child often walks on tiptoe because of the increased tone in the antigravity gastrocnemius muscles, and the affected upper extremity assumes a flexed posture



**Fig. 2:** Cerebral palsy with microcephaly.



**Fig. 3:** Cerebral palsy.



**Fig. 4:** Scissoring of lower limb.

when the child runs. Ankle clonus and a Babinski sign may be present, the deep tendon reflexes are increased, and weakness of the hand and foot dorsiflexors is evident.

Infants with spastic hemiplegia have decreased spontaneous movements on the affected side and show hand preference at a very early age. The arm is often more involved than the leg and difficulty in hand manipulation is obvious by 1 year of age. Walking is usually delayed until 18–24 months, and a circumductive gait is apparent. Examination of the extremities may show growth arrest, particularly in the hand and thumbnail, especially if the contralateral parietal lobe is abnormal, because extremity growth is influenced by this area of the brain.

## Spastic Diplegia

Common in premature infants, patients with diplegic cerebral palsy usually will have low tone for the first few months, followed by increased muscle tone that is more apparent in their legs than their arms. These patients, if ambulatory, will often toe walk. Contractures commonly develop in the hips and hamstrings.

Spastic diplegia is bilateral spasticity of the legs that is greater than in the arms. Spastic diplegia is strongly associated with damage to the immature white matter during the vulnerable period of immature oligodendroglia between 20 and 34 weeks of gestation.

The first clinical indication of spastic diplegia is often noted when an affected infant begins to crawl. The child uses the arms in a normal reciprocal fashion but tends to drag the legs behind more as a rudder (commando crawl) rather than using the normal 4-limbed crawling movement. If there is paraspinal muscle involvement, the child may be unable to sit.

Examination of the child reveals spasticity in the legs with brisk reflexes, ankle clonus, and a bilateral Babinski sign. When the child is suspended by the axillae, a scissoring posture of the lower extremities is maintained. Walking is significantly delayed, the feet are held in a position of equinovarus, and the child walks on tiptoe.

Severe spastic diplegia is characterized by disuse atrophy and impaired growth of the lower extremities and by disproportionate growth with normal development of the upper torso. The prognosis for normal intellectual development for these patients is good, and the likelihood of seizures is minimal. Such children often have learning disabilities and deficits in other abilities, such as vision, because of disruption of multiple white matter pathways that carry sensory as well as motor information.

The most common neuropathologic finding in children with spastic diplegia is PVL, which is visualized on MRI in more than 70% of cases. MRI typically shows scarring and shrinkage in the periventricular white matter with compensatory enlargement of the cerebral ventricles.

## Spastic Quadriplegia

Spastic quadriplegia is the most severe form of CP because of marked motor impairment of all extremities and the high association with intellectual disability and seizures. Swallowing difficulties are common as a result of supranuclear bulbar palsies, often leading to aspiration pneumonia. The most common lesions seen on pathologic examination or on MRI scanning are severe PVL and multicystic cortical encephalomalacia.

Diffuse spasticity (sometimes more prominent on one side of the body than the other) is present in patients with quadriplegic cerebral palsy. These patients typically have truncal dystonia, intellectual disability, hyperreflexia, and progressive contractures leading to loss of range of motion in all limbs. This type of cerebral palsy is commonly seen in term or near-term infants who experience a hypoxic ischemic injury at birth or when there are bilateral large-vessel strokes.

Neurologic examination shows increased tone and spasticity in all extremities, decreased spontaneous movements, brisk reflexes, and plantar extensor responses. Flexion contractures of the knees and elbows are often present by late childhood. Associated developmental disabilities, including speech and visual abnormalities, are particularly prevalent in this group of children. Children with spastic quadriplegia often have evidence of athetosis and may be classified as having mixed CP.

The associated sensory deficit may be as detrimental to ultimate function as is spasticity and motor deficit. The child often ignores the affected side. Perpetual and learning problems, astereognosis and seizures are common associated problems.

Sensory deficits of cortical type such as two point discrimination and astereognosis on the affected side are observed. Homonymous hemianopia is frequently present but rarely cause a disability. Speech and language disorders are seen with both left as well as right hemiplegia. Mental retardation is less common in hemiplegic cerebral palsy.

On ventral suspension, the infant goes into an extensor posture and does not reflex his knees or

thighs. Severely handicapped children may be in a position of opisthotonus. They may have variable degree of mental, visual handicaps and behavioral problems. Seizures are common in all infants and require treatment.

### POSTER CRITERIA OF CEREBRAL PALSY

- *Posturing:* Abnormal movements
- Oropharyngeal problems
- Strabismus
- *Tone:* Hyper/Hypo
- *Evolutional maldevelopment:* Persistence of primitive reflexes
- *Reflexes:* Increased deep tendon reflexes/persistent Babinski's reflex

*Any of the four criteria suggests cerebral palsy*

## Dyskinetic Cerebral Palsy

When injury is predominantly to the deep gray matter, such as in kernicterus, the patient's predominant symptoms will be abnormal movements. They can include dystonia, chorea, athetosis, and myoclonus.

This pattern of cerebral palsy is often noticed around the first birthday as the movements are typically exacerbated by voluntary motor activities (reaching, crawling and walking). Patients with dyskinetic syndromes will also often have speech abnormalities. Symptoms tend to be exacerbated by stress, fatigue, anxiety, or intercurrent illness.

Athetoid CP, also called choreoathetoid, extra-pyramidal, or dyskinetic CP, is less common than spastic CP and makes up approximately 15–20% of patients with CP. Affected infants are characteristically hypotonic with poor head control and marked head lag and develop variably increased tone with rigidity and dystonia over several years.

The term dystonia refers to the abnormality in tone in which muscles are rigid throughout their range of motion and involuntary contractions can occur in both flexors and extensors leading to limb positioning in fixed postures. Unlike spastic diplegia, the upper extremities are generally more affected than the lower extremities in extra-pyramidal cerebral palsy.

Feeding may be difficult, and tongue thrust and drooling may be prominent. Speech is typically affected because the oropharyngeal muscles are involved. Speech may be absent or sentences are slurred, and voice modulation is impaired. Generally, upper motor neuron signs are not present, seizures are uncommon, and intellect is preserved in many patients.

The choreoathetoid cerebral palsy is associated with neonatal hyperbilirubinemia and the pathologic correlate is selective involvement of central grey nuclei. The dystonic type is associated with hypoxia and neuropathologic correlate is status marmoratus– marbled appearance of basal ganglia, which results from diffuse gliosis.

Associated problems include severely impaired speech and oromotor problems. High frequency hearing loss is common in patients with dyskinetic cerebral palsy related to erythroblastosis fetalis. Intelligence is normal in most of the patients and epilepsy is less common in this type. Speech is usually impaired due to the involvement of buccopharyngeal muscles and drooling may be a major problem.

Ataxic Cerebral Palsy

The motor disorder is cerebellar ataxia due to nonprogressive lesion of brain. The etiology of pure ataxic cerebral palsy is different from other types in that genetic factors are important. Developmental anomalies of cerebellum are often seen on neuroimaging.

The etiology of pure ataxic CP is different from other types in that genetic factors are important. Developmental anomalies of the cerebellum are seen. There is initial stage of hypotonia and delayed motor milestones. This is followed by the appearance of truncal ataxia and intention tremor or the ataxic stage. It is characterized by low postural tone and disturbed equilibrium. Wide based gait imbalances on standing are noted.

Typical nystagmus is not common but strabismus and poor eye tracking may be seen in some cases. Ataxia is often accompanied with spastic diplegia. Associated problems include delay and articulation defects in speech, intellectual impairment and epilepsy.

Mixed Type

It is the term used to indicate any child who shows features of more than one type of cerebral palsy. The most common combination is that of spastic diplegia with dyskinesia. Children with ataxic form often have diplegia-ataxic diplegia.

Hypotonic cerebral palsy is a transient stage in infancy in the evolution of spasticity or dyskinetic variety of cerebral palsy.

Hypotonic Syndromes

Initially after a hypoxic injury, neonates will typically exhibit low muscle tone, which often

progresses over time to spasticity. It may be difficult initially to detect reflexes in hypotonic infants. Prematurity can also cause delayed milestones, so using corrected gestational age and performing serial assessments is important. If hypotonia persists, patients will continue to have diminished or absent reflexes, marked weakness of the legs, and arms with low muscle tone more pronounced than weakness. This is the rarest type of cerebral palsy. It is important in these patients to exclude similar diagnoses including lower motor neuron diseases, metabolic disorders, neurodegenerative diseases, or genetic conditions that predispose to low tone such as Down syndrome, Prader-Willi syndrome, and Angelman syndrome.

ASSOCIATED PROBLEMS IN CHILDREN WITH CEREBRAL PALSY	
<i>Neurological:</i> <ul style="list-style-type: none"><li>• Mental retardation</li><li>• Cortical sensory deficits</li><li>• Visual and hearing problems</li><li>• Epilepsy</li><li>• Communication disorders</li></ul> <i>Gastrointestinal:</i> <ul style="list-style-type: none"><li>• Oropharyngeal dysphagia</li><li>• Gastroesophageal reflux</li><li>• Constipation</li><li>• Malnutrition</li><li>• Drooling of saliva</li></ul>	<i>Orthopedic:</i> <ul style="list-style-type: none"><li>• Equinus</li><li>• Hip subluxation/ dislocation</li><li>• Scoliosis</li><li>• Hamstring contracture</li></ul> <i>Miscellaneous:</i> <ul style="list-style-type: none"><li>• Sleep problems</li><li>• Lower urinary tract dysfunction</li><li>• Emotional and behavioral problems</li></ul>

GROSS MOTOR DELAYS ASSOCIATED WITH CEREBRAL PALSY
<ul style="list-style-type: none"><li>• Unable to bring both the hands together by the age of 4 months</li><li>• Head lag persisting beyond 6 months</li><li>• No volitional rolling by 6 months</li><li>• Unable to sit without support by 8 months</li><li>• No hands to knee crawling by 12 months</li></ul>

GENERAL FEATURES
<ul style="list-style-type: none"><li>• Presence of primitive reflexes</li><li>• Quadriplegia</li><li>• Diplegia</li><li>• Pseudobulbar palsy</li></ul>

DIAGNOSIS

A thorough history and physical examination should preclude a progressive disorder of the CNS, including degenerative diseases, metabolic disorders, spinal cord tumor, or muscular dystrophy. The possibility of anomalies at the base of the skull or other disorders affecting the cervical spinal cord needs to be considered in patients

with little involvement of the arms or cranial nerves.

The diagnosis is suspected when early growth and development is delayed. Evaluation includes perinatal history, detailed neurological and developmental examination, electroencephalogram, psychomotor and sensory evaluation. Precise etiological diagnosis should be sought for the progressive lesion.

An MRI scan of the brain is indicated to determine the location and extent of structural lesions or associated congenital malformations. MRI scan of the spinal cord is indicated if there is any question about spinal cord pathology. If the MRI is abnormal, the location and degree of abnormalities are considered as to whether they are consistent with the clinical presentation. If migrational abnormalities are present, consideration should be made for a genetic cause. When the distribution of damage is concerning for a, vascular lesion, coagulopathy workup should be performed, and the patient should be referred for hematology. In the case of normal imaging, further evaluation should be pursued in order to ensure that a mimic of cerebral palsy, for example a genetic or metabolic disorder or neuromuscular disease, is not present. There are rare cases of “MRI-negative” cerebral palsy, but it should be a diagnosis of exclusion. Additional studies may include tests of hearing and visual function.

Genetic evaluation should be considered in patient with congenital malformations (chromosomes) or evidence of metabolic disorders (e.g., amino acids, organic acids, MR spectroscopy). In addition to the genetic disorders mentioned earlier that can present as CP the urea cycle disorder arginase deficiency is a rare cause of spastic diplegia and a deficiency of sulfite oxidase or molybdenum cofactor can present as CP caused by perinatal asphyxia. Tests to detect inherited thrombophilic disorders may be indicated in patients in whom an in utero or neonatal stroke is suspected as the cause of CP.

Inborn errors of metabolism such as aminoaciduria should be excluded by chromatography of the plasma and urine. The diagnosis of the cerebral palsy should be suspected if child with low birth weight, perinatal insult has increased tone, feeding difficulties.

## Electroencephalogram

Infants with cerebral palsy are at higher risk than the general population to have seizures, and up to 50% of patients, depending on the location of their

lesion and type of cerebral palsy, will have at least one seizure in their lifetime: Evaluation for seizure predisposition with electroencephalogram (EEG) is not routinely indicated in patients with cerebral palsy; thus, consideration of EEG should be on a case-by-case basis.

## Genetic Testing

Genetic testing is not indicated routinely in patients with cerebral palsy. However, in individuals in whom the neonatal course or imaging is not consistent with symptomatology, in patients with regression, or in families with a strong history of children with a diagnosis of cerebral palsy, referral to genetics should be placed. Typical testing will include chromosome microarray, often followed by whole-exome sequencing, although more targeted testing may be performed based on the patient's phenotype.

### LABORATORY SALIENT FINDINGS

- MRI
- CT scan: Periventricular calcification
- IgG, IgM, antibody levels
- Blood: Aminoacids, lactate, pyruvate, and ammonia concentrate
- Urine: Amino acids, and organic acids

## DIFFERENTIAL DIAGNOSIS

- Hydrocephalus with subdural effusion
- Intracranial space occupying lesion (ICSOL)
- Muscular dystrophy
- Ataxia telangiectasia
- Leucodystrophies
- Spinal cord lesions

## TREATMENT

Progress has been made in both prevention of CP before it occurs and treatment of children with the disorder. Preliminary results from controlled trials of magnesium sulfate given intravenously to mothers in premature labor with birth imminent before 32 weeks gestation showed significant reduction in the risk of CP at 2 years of age.

To treat a child with cerebral palsy one must evaluate the different possible malfunctions of the system. Ability to relate sensory input to motor input forms the basis of posture control development. Coupling visual and non-visual information is crucial to developing and maintaining movements. The therapy aims at:

- Reduction of spasticity
- Prevention of abnormal posture
- Prevention of contractures and deformities



- Inhibition of primitive reflexes and facilitation of normal patterns of movement
- Stimulation of sensory, cognitive and perceptual functions

With neurodevelopmental therapy has the widest appeal all over, many therapists use an eclectic approach to treatment. They first evaluate the patient's deficits and needs and then choose a variety of modalities from the established modalities tailoring it to the needs of the child.

Children with spastic diplegia are treated initially with the assistance of adaptive equipment, such as walkers, poles, and standing frames. If a patient has marked spasticity of the lower extremities or evidence of hip dislocation, consideration should be given to performing surgical soft tissue procedures that reduce muscle spasm around the hip girdle, including an adductor tenotomy or psoas transfer and release.

A rhizotomy procedure in which the roots of the spinal nerves are divided produces considerable improvement in selected patients with severe spastic diplegia. A tight heel cord in a child with spastic hemiplegia may be treated surgically by tenotomy of the Achilles tendon.

Quadriplegia is managed with motorized wheelchairs, special feeding devices, modified typewriters, and customized seating arrangements. The function of the affected extremities in children with hemiplegic CP can often be improved by therapy in which movement of the good side is constrained with casts while the impaired extremities perform exercises which induce improved hand and arm functioning. This constraint-induced movement therapy is effective in patients of all ages.

## **MEDICAL MANAGEMENT**

### **Respiratory**

Individuals with cerebral palsy are at a high risk for aspiration, and lung disease often is a cause of significant morbidity and mortality. Factors that increase the risk of choking include poor swallowing, increased secretions, scoliosis, and airway obstruction. It is important to obtain proper studies such as swallow studies to evaluate for aspiration, sleep studies to evaluate for central or obstructive sleep apnea, and routine films for scoliosis monitoring to ensure appropriate interventions are being performed. Patients may benefit from chest physiotherapy and bronchodilators to help with clearance of secretions, noninvasive respiratory support such as continuous positive

airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) to help with sleep-disordered breathing, and scoliosis surgery to help with restrictive lung disease. Medications for secretions and reflux can also help to prevent aspirations.

### **Circulatory**

Patients can have issues with their peripheral circulation as a result of poor mobility and will often have cold or discolored extremities. Congenital heart disease can lead to neonatal stroke, which can predispose to cerebral palsy. Patients with neonatal stroke also may have a coagulopathy leading to their symptoms and should undergo hematologic evaluation.

### **Gastrointestinal**

Swallowing difficulty is a common problem in patients with cerebral palsy for several reasons. During the infancy period, patients may have issues coordinating a strong suck and swallow. As patients get older, swallowing issues may lead to pooling of secretions and profuse drooling. It is important to perform swallow studies and modify diet as needed to help prevent aspiration. Medications such as glycopyrrolate or scopolamine can also be helpful to treat drooling, and in some individuals with refractory secretions, botulinum toxin injections or ablation of the salivary glands is indicated.

Constipation is another frequent issue, often due to immobility and dehydration. Patients may also have constipation as a side effect of medications to help decrease secretions. Use of conservative measures such as prune juice, medications such as laxatives or stool softeners, or in some cases suppositories or enemas is helpful in maintaining a normal bowel regimen.

### **Nutrition**

Failure to thrive is another common issue, due to increased metabolic demand in the spastic patient, swallowing issues as noted earlier, and decreased gastric motility leading to prolonged feeding times. Growth parameters need to be monitored closely, and evaluation by a nutritionist is often indicated. Some patients require a gastrostomy tube either due to lengthy time required for meals, aspiration with oral intake, or difficulty maintaining a healthy weight. Avoidance of malnutrition is important as this increases risk for development of illness, fractures, and skin breakdown, and can lead to a decrease in life expectancy.

## Neurologic

The neurologic status of patients with cerebral palsy varies widely, from individuals with normal intelligence' and no seizures to patients who are profoundly intellectually disabled and have medically refractory epilepsy. The location and extent of the anatomic lesion in the brain may be helpful in some cases to predict the degree of neurologic involvement, although it is important to prognosticate on a case-by-case basis.

Almost half of patients with cerebral palsy will have epilepsy, most commonly patients with hemiplegic or quadriplegic syndromes. EEGs must be obtained to evaluate patients with suspected seizures, and appropriate antiepileptic medications should be prescribed. Some medications such as the benzodiazepines can be used for the dual purpose of managing muscular tone and preventing seizures. Side effects of medications should be monitored closely as many seizure medications can cause cognitive slowing drowsiness, or anorexia, which often exacerbates preexisting problems in patients with cerebral palsy.

Abnormal movements, including myoclonic jerks, startle myoclonus, opisthotonic posturing, chorea, and athetosis, are seen frequently in patients with cerebral palsy. Some of the movements may mimic seizures, and differentiating between a movement disorder and seizure disorder often requires prolonged EEG monitoring. Treatment for movement disorders can include oral medications or, in some refractory cases, deep brain stimulation.

Intellectual disability can occur in as many as half of patients with cerebral palsy. It is important to discern whether a true intellectual disability is present or whether a communication difficulty is preventing the patient from performing at his or her full ability. Dysarthria, present in many patients, can make it very difficult for patients to express themselves, and these patients benefit greatly from augmentative communication devices. Assessment by developmental pediatricians is helpful to establish developmental quotient and appropriate school modifications. Patients may also have associated hearing and vision deficits, and screening should be performed so that interventions can be performed at an early age. Evaluation for attention deficit disorders, autistic spectrum disorders, and mood disorders may also be indicated.

## Genitourinary

Issues with urination, including incontinence and retention, can be the result of intellectual

disability, poor voluntary muscle control, mobility issues, or inability to process sensory feedback. If urinary continence is achieved, it may be delayed. Some patients will require intermittent catheterization to prevent sequelae of urinary retention, which can include increased risk for urinary tract infections, overflow incontinence, and kidney damage from vesicoureteral reflux. Medications used to treat other symptoms can cause urologic symptoms (e.g., urinary retention with anticholinergic medications for treatment of drooling or dystonia and renal stones with certain antiepileptic medications).

## Musculoskeletal

Patients with cerebral palsy, especially those who are unable to ambulate, are at risk for developing contractures, bony deformities, and joint pain. Exercise, if possible, is helpful to try to prevent these changes. Treatment for increased muscle tone with stretching, medications, injections, and braces is also helpful to preserve range of motion. It is important to perform surveillance imaging of the spine and hips to evaluate for scoliosis and hip dislocation, which can be a source of discomfort. Osteopenia and fractures are another risk, and patients are often treated with vitamin D and calcium to help improve bone density. Bisphosphonates are another option but are not widely used due to side effect concerns.

## Orthopedic Management

The judgment of when to operate and the type of procedure is the key to orthopedic care. For hip subluxation abduction splinting or surgery may be required. This consists of adductor tenotomies-myotomies.

Osteotomies may be necessary in advanced cases. Tendo Achilles contracture is treated by bracing, casting or surgical procedure. Treatment of scoliosis can be nonoperative such as bracing or by surgical stabilization depending on the severity.

## Neurosurgery

The disability in children with cerebral palsy is often attributed to concomitant spasticity. Partial division of posterior lumbar roots or selective dorsal rhizotomy (SDR) has become a common surgical treatment to reduce spasticity. The technique involves bilateral isolation of the posterior roots from L2 to S1 and stimulation of each root with EMG and direct observation of sustained muscle contraction in order to decide which rootlets to divide.

## Rehabilitation

For a child with cerebral palsy, infancy is the time during which process of rehabilitation is set on a firm footing since it during this crucial period that the patient are likely to raise concern regarding the child's development. The medical professionals play an important role in communicating the diagnosis and counseling parents regarding treatment. The goal of rehabilitation is to achieve promotion of motor and functional development and independence as far as possible in activities of daily living and to prepare the child for schooling depending upon his mental status.

## Physiotherapy

The physiotherapists help in improving the motor and functional skills and locomotion as well as prevention of contractures and deformities. Physiotherapy aims at reducing abnormal patterns of movements and posture and to promote the normal ones so as to enable the child to gain maximal functional independence. The rationale for early physiotherapy in cerebral palsy is based on plasticity of brain.

The role of physiotherapy and occupational therapy is closely linked and both have to work at the same goal. The occupational therapist advises the parents on activities of daily living—bathing, feeding and dressing.

## Speech Therapy

The speech therapist also helps in developing an effective feeding program along with occupational therapist. Appropriate positioning of head and jaw is basic to both feeding and speech. The inhibition of abnormal oral reflexes is necessary for feeding. Speech therapists employ auditory stimulation and work for improvement of muscle control required for feeding and articulation.

## MEDICATIONS

### Antiepileptic Drugs

A very high incidence of west syndrome has been observed in patients with spastic quadriplegia. The guidelines of stopping the therapy are similar to the general population but only a 1/5th of the patients may achieve remission and withdrawal of medication. Tiagabine—a newer antiepileptic drug has been shown to bring about seizure control as well as reduction in spasticity with improvement in function.

### Antispasticity Drugs

Several drugs have been used to treat spasticity, including the benzodiazepines and baclofen. These medications have beneficial effects in some patients but can also cause side effects such as sedation for benzodiazepines and lowered seizure threshold for baclofen. Several drugs can be used to treat spasticity, including oral diazepam (0.01–0.3 mg/kg/day, divided bid or qid), baclofen (0.2–2 mg/kg/day, divided bid or tid) or dantrolene (0.5–10 mg/kg/day, bid). Small doses of levodopa (0.5–2 mg/kg/day) can be used to treat dystonia or DOPA responsive dystonia. Artane (trihexyphenidyl, 0.25 mg/day, divided bid or tid and titrated upward) is sometimes useful for treating dystonia and can increase use of the upper extremities and vocalizations. Reserpine (0.01–0.02 mg/kg/day, divided bid to a maximum of 0.25 mg daily) or tetrabenazine (12.5–25.0 mg, divided bid or tid) can be useful for hyperkinetic movement disorders including athetosis or chorea.

Antispasticity drugs like baclofen, dantrolene and diazepam bring limited benefit since although these reduce spasticity there is no improvement in co-ordination. Baclofen works primarily at spinal cord level through a presynaptic GABA receptor-GABA subtype.

It is started at the dose of 2.5 mg twice daily and increased every 3–5 days up to 2 mg/kg (maximum 70 mg) divided in 3–4 doses. It is important to strike a balance between relaxation and spasticity so that child does not lose his functional capacity secondary to excessive relaxation.

### Medication for Excessive Salivation

Benztropine may be used in patients with excessive drooling.

### Medications for Dystonia

Levodopa may be tried in cases with severe athetosis. Athetosis in dyskinetic cerebral palsy may respond to treatment with benzodiazepines also. Trihexyphenidyl and carbamazepine may be useful in patients with severe dystonia. Since all these drugs are accompanied with side effects these medications should be used only in patients in whom involuntary movements are persistent and disabling.

## PROGNOSIS

Parents of the affected child generally want to know whether and when the child will be able to walk and what the future holds for him.

The type and severity of cerebral palsy are useful guides in predicting ambulation.

Most children with spastic hemiplegia have walked by 2 years and all walked by 3 years. Similarly all children with ataxic cerebral palsy will walk although much later than those with spastic hemiplegia. Of children spastic diplegia, 65% will walk unassisted and 20% with the help of assistive devices.

Children with quadriparesis have a poorer prognosis. The presence of primitive reflexes at 2 years was highly associated with nonambulatory skills at 8 years. All children who can sit by 2 years will eventually walk.

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# Duchenne Muscular Dystrophy

## PRESENTING COMPLAINTS

A 6-year-old boy was brought with the complaints of:

- Abnormal walking posture since 2 years
- Difficulty in getting up since 2 months

## History of Presenting Complaints

A 6-year-old boy was brought to the hospital with history of abnormal gait. Parents noticed that his son's gait was not normal. Gait was becoming more abnormal as the days passed. Mother informed that her son found very difficult to get up from the sitting up posture. He was taking the help of the objects to get up. He was not able to play or run as other kids were doing. Parents also told that they noticed this abnormal gait when he was 2-year-old.

## Past History of the Patient

He was the elder sibling of nonconsanguineous marriage. He was born at term by normal delivery. He cried immediately after the delivery. He had transient tachypnea which settled by itself within 24 hours. The birth weight of the child was 3 kg. The child was on breast milk immediately after

the delivery. He was on breast milk exclusively for 3 months. Weaning was started at the age of 4 months. He was on family food by the age of 10 months. Mother had noticed that he had difficulty in climbing the stairs. He was not able to run or hop. He used to frequently fall.

## EXAMINATION

On examination, the child was moderately built and nourished. He was sitting on the table with his hands supporting on the thighs. Anthropometric measurements included, the height was 114 cm (50th centile), and the weight was 18 kg (60th centile). He was afebrile. The pulse rate was 110 per minute. The respiratory rate was 20 per minute. The blood pressure recorded was 70/50 mm Hg. There was no pallor, no lymphadenopathy, and no edema.

His posture showed marked lumbar lordosis. There were hypertrophied calf muscles. The child had difficulty in getting up from the sitting posture. He had flat foot. He was making use of his own thigh and furniture to get up from the sitting posture. There was symmetrical proximal muscle weakness. All the systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 6,000 cells/cu mm
ESR	: 26 mm in the 1st hour
CPK	: 1000 U/L
LDH	: 800 U/L
Muscle biopsy	: Suggestive of primary muscular disease

## DISCUSSION

The boy presented with history of abnormal gait with delayed motor milestones, and symmetrical proximal muscle weakness gives the suspicion of Duchenne muscular dystrophy (DMD). The diagnosis is again supported by presence of hypertrophied calf muscle and lordosis. Laboratory investigations such as creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) levels are

### CASE AT A GLANCE

#### Basic Findings

Height	: 114 cm (50th centile)
Weight	: 18 kg (60th centile)
Temperature	: 37°C
Pulse rate	: 110 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Abnormal gait

##### Examination

- Hypertrophy of calf muscles
- Proximal muscle weakness

##### Investigation

- CPK: 1000 U/L
- LDH: 800 U/L
- Muscle biopsy: Suggestive of primary muscle disorders



grossly elevated. Muscle biopsy suggests primary muscular disease.

Duchenne muscular dystrophy is the most common hereditary neuromuscular disease affecting all races and ethnic groups. Its characteristic clinical features are progressive weakness, intellectual impairment, hypertrophy of the calves, and proliferation of connective tissue in muscle. The incidence is 1 in 3,600 liveborn infant boys. This disease is inherited as an X-linked recessive trait. The abnormal gene is at the Xp21.1-Xp21.2 locus and is one of the largest genes. Becker muscular dystrophy (BMD) is a disease that is fundamentally similar to DMD, with a genetic defect at the same locus, but clinically it follows a milder and more protracted course. The associated pathological changes in the muscle due to deficiency of protein dysmorphia.

### CLINICAL FEATURES (FIG. 1)

Duchenne muscular dystrophy is the most common hereditary neuromuscular disease. It is inherited as X-linked recessive trait.

Infant boys are rarely symptomatic at birth or in early infancy, although some are mildly hypotonic. Early gross motor skills, such as rolling over, sitting, and standing, are usually achieved at the appropriate ages or may be mildly delayed.

Early development of the child is normal or slightly delayed. Poor head control in the infancy may be the first sign of weakness. Hip girdle weakness may be seen in subtle forms at the age of 2 years. By the age of 2nd year, child may appear clumsy while walking. Hypertrophy of the calf muscle may be observed at the age of 4–5 years.

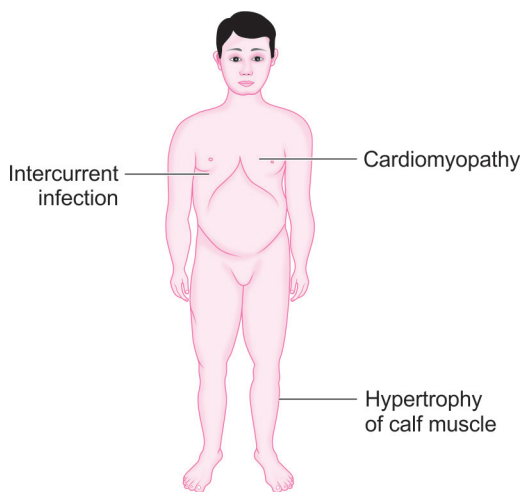


Fig. 1: Clinical features.

The older children may assume lordotic postures. When standing to compensate gluteal muscle weakness, waddling gait, difficulty in climbing the stair, and hypertrophy of calf muscles are the common presentation. Enlargement of the calves (pseudohypertrophy) and wasting of thigh muscles are classic features. The enlargement is caused by hypertrophy of some muscle fibers, infiltration of muscle by fat, and proliferation of collagen. After the calves, the next most common site of muscular hypertrophy is the tongue, followed by muscles of the forearm. Other muscles which get hypertrophied are deltoid and brachioradialis.

Early in the disease, the hypertrophied muscles are often strong, but later the muscles become weak. The hypertrophied calf muscles are stronger than the anterior leg muscles. Hence toe walking will be there. This leads to the contraction of heel cord.

Weakness of pelvic muscles produces waddling lordotic gait and difficulty in rising from the floor. When gets up from the floor, he first rolls to prone position, kneels and then arises himself to stand by pushing his hands against shin, knee and thighs. He stands up, he climbs upon his own body by supporting it with his hands—Gower's sign (Fig. 2). It indicates weakness in pelvic girdle muscle.

Gower's sign is often evident by age 3 years and is fully expressed by age 5 years or 6 years. A Trendelenburg gait, or hip waddle, appears at this time. Common presentations in toddlers include delayed walking, falling, toe walking, and trouble running or walking upstairs, developmental delay and, less often, malignant hyperthermia after anesthesia.



Fig. 2: Gower's sign.

**ESSENTIAL DIAGNOSTIC POINTS**

- Delayed motor milestones
- Symmetrical proximal muscle weakness
- Lordosis
- Gower's sign
- Increased CPK, LDH, levels
- Cardiomyopathy
- No mental debility

Forced vital capacity is reduced in these patients due to scoliosis. These children are more prone to develop aspiration pneumonia due to esophageal reflux because of distortion of diaphragm.

In the late teens or early 20s respiratory failure may occur as a result of increasing nocturnal hypoventilation and hypoxia. Higher incidences of emotional disturbances are seen. It is accompanied by cerebral atrophy as demonstrated by CT scan.

Cardiomegaly, persistent tachycardia and cardiomyopathy are constant features. ECG changes are often present. Severe peripheral circulatory failure may follow aspiration. Facial features include wide arch of mandible and with wide separation of teeth which may be due to macroglossia.

Cardiomyopathy, including persistent tachycardia and myocardial failure, are seen in 50–80% of patients with this disease. The severity of cardiac involvement does not necessarily correlate with the degree of skeletal muscle weakness. Some patients die early of severe cardiomyopathy while still in ambulatory stage; and others in terminal stages of the disease.

Contractures most often involve the ankles, knees, hips, and elbows. Scoliosis is common. The thoracic deformity further cardiopulmonary capacity and compromises the heart. Scoliosis usually progresses more rapidly after the child becomes nonambulatory and may be uncomfortable or painful.

Ambulation is important not only for postponing psychological depression but also to prevent scoliosis. Scoliosis often becomes rapidly progressive after confinement to wheelchair. There is a tendency to walk on toes and calf muscles are prominent and hence pseudohypertrophy.

Ankle jerks are brisk and knee jerks are sluggish. It resembles clinically chronic spinal atrophy, dermatomyositis, limb girdle and muscular dystrophy.

The relentless progression of weakness continues into the second decade. The function of distal muscles is usually relatively well enough preserved, allowing the child to continue to use eating utensils, a pencil, and a computer keyboard.

Respiratory muscle involvement is expressed as a weak and ineffective cough, frequent pulmonary infections, and decreasing respiratory reserve. Pharyngeal weakness can lead to episodes of aspiration, nasal regurgitation of liquids, and nasal voice quality. The function of the extraocular muscles remains well preserved. Incontinence due to anal and urethral sphincter weakness is an uncommon and very late event.

**GENERAL FEATURES**

- Appears clumsy while walking
- Falls easily
- Difficulty in climbing up the stair
- Gower's sign
- Weakness of pelvic girdle muscle

**DIAGNOSIS**

Polymerase chain reaction (PCR) for the dystrophin gene mutation is the primary test, if the clinical features and serum CPK are consistent with the diagnosis. If the blood PCR is diagnostic, muscle biopsy may be deferred. But if it is normal and clinical suspicion is high, the more specific dystrophin immunocytochemistry is performed on muscle biopsy sections. This detects the 30% of cases that do not show PCR abnormalities.

The muscle biopsy is diagnostic and shows characteristic changes. Myopathic changes include endomysial connective tissue proliferation, scattered degenerating and regenerating myofibers, foci of mononuclear inflammatory cell infiltrates as a reaction to muscle fiber necrosis, mild architectural changes in still, functional muscle fibers, and many dense fibers. These hypercontracted fibers probably result from segmental necrosis at another level allowing calcium to enter the site of breakdown of the sarcolemmal membrane and trigger a contraction of the whole length of the muscle fiber. Calcifications within myofibers are correlated with secondary beta-dystroglycan deficiency.

The serum CPK level is consistently greatly elevated in DMD, even in presymptomatic stages, including at birth. The usual serum concentration is 15,000–35,000 IU/L (normal <160 IU/L). A normal serum CK level is incompatible with the diagnosis of DMD, although in terminal stages of the disease, the serum CPK value may be considerably lower than it was a few years earlier because there is less muscle to degenerate. Other lysosomal enzymes present in muscle, such as aldolase and aspartate aminotransferase, are also increased but are less specific.

Cardiac assessment is done by echocardiography and electrocardiograms and chest radiography. ECG shows minor abnormalities in 70% of cases.

Electromyogram (EMG), shows characteristic myopathic features, a normal interference pattern. There is no spontaneous activity at rest and low amplitude, short duration polyphasic motor units on stimulation.

Muscle biopsy shows a wider than normal variation in fiber diameter, internal nuclei opaque fibers and increased fat and connective tissues.

#### LABORATORY SALIENT FINDINGS

- Elevated CPK
- Elevated LDH
- ECG, ECHO
- Chest X-ray
- Electromyogram
- Muscle biopsy

**Carrier detection:** Ten percent of carriers at least manifest a few clinical signs with varying degree of muscle weakness due to ionization, 45X chromosomal status or autosomal translocation. Muscle biopsy may reveal myopathic changes in a third of carriers.

Chorionic villus sample taken around 10 weeks of gestation is subjected for rapid fetal sexing as well as DNA studies.

### DIFFERENTIAL DIAGNOSIS

- Polyneuritis
- Chronic spinal muscular atrophy
- Dermatomyositis
- Myelopathies

### TREATMENT

There is no medical cure for this disease. Much can be done to treat complications and to improve the quality of life of affected children. Cardiac decompensation often responds initially well to digoxin. Pulmonary infections should be promptly treated. Patients should avoid contact with children who have obvious respiratory or other contagious illnesses. Immunizations for influenza virus and other routine vaccinations are indicated.

Preservation of a good nutritional state is important. DMD is not a vitamin-deficiency disease, and excessive doses of vitamins should be avoided. Adequate calcium intake is important to minimize osteoporosis in boys confined to a wheelchair, and fluoride supplements may also be given, particularly if the local drinking water is not fluoridated.

Physiotherapy delays but does not always prevent contractures. At times, contractures are actually useful in functional rehabilitation. If contractures prevent extension of the elbow beyond 90° and the muscles of the upper limb no longer are strong enough to overcome gravity the elbow contractures are functionally beneficial in fixing an otherwise flail arm and in allowing the patient to eat and write. Surgical correction of the elbow contracture may be technically feasible, but the result may be deleterious. Physiotherapy contributes little to muscle strengthening because patients usually are already using their entire reserve for daily function, and exercise cannot further strengthen involved muscles. Excessive exercise can actually accelerate the process of muscle fiber degeneration.

Another recommended treatment of patients with DMD involves the use of prednisone, prednisolone, deflazacort, or other steroids. Glucocorticoids decrease the rate of apoptosis or programmed cell death of myotubes during ontogenesis and can decelerate the myofiber necrosis in muscular dystrophy. Strength usually improves initially, but the long-term complications of chronic steroid therapy, including considerable weight gain and osteoporosis, can offset this advantage or even result in greater weakness than might have occurred in the natural course of the disease.

Nevertheless, some patients with DMD treated early with steroids appear to have an improved long-term prognosis in muscle and myocardial outcome, as well as short-term improvement muscle strength, and steroids can help keep patients ambulatory for more years than expected without treatment. One protocol gives prednisolone (0.75 mg/kg/day) for the first 10 days of each month to avoid chronic complications. Deflazacort, administered as 0.9 mg/kg/day, may be more effective than prednisone. Fluorinated steroids, such as dexamethasone or triamcinolone, should be avoided because they induce myopathy by altering the myotube abundance of ceramide.

Newer therapies include exon skipping using antisense oligonucleotides. Phase 3 trials have shown significant clinical benefits. Eteplirsen has FDA approved.

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## PRESENTING COMPLAINTS

An 8-year-old boy was brought with the complaints of:

- Cough and cold since 1 week
- Fever since 1 week
- Headache since 1 week
- Abnormal movements of limbs since 2 hours

## History of Presenting Complaints

An 8-year-old boy was brought to pediatric casualty department. With history of abnormal movements involving both upper limb and lower limb. There was also uprolling of eyeballs. According to the mother, her son became unconscious simultaneously with abnormal movements. That was associated with froth in the mouth. According to the mother, her son has been treated for cough, cold and fever about 10 days back. She also recollected that her son used to get repeated attacks of headache recently. There was no history of similar attacks before.

### CASE AT A GLANCE

#### Basic Findings

Height	: 126 cm (70th centile)
Weight	: 22 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 110 per minute
Respiratory rate	: 24 per minute
Blood pressure	: 90/70 mm Hg

#### Positive Findings

##### History

- Abnormal movements
- Uprolling of eyeball
- Unconscious

##### Examination

- Convulsions
- Tongue bite
- Crepitation in chest
- Abdominal distension
- Normal nervous system

##### Investigation

- Chest X-ray: Shows patchy pneumonitis
- EEG: Shows random spikes

## Past History of the Patient

He was the second child of consanguineous marriage. He was delivered at full-term by normal vaginal delivery. Delivery was uneventful. He was on breastfeed exclusively for 6 months. Later weaning was started and was on family food by 10 months. He had been completely immunized. His developmental milestones were normal. His scholastic performance was good. His sister was 11-year-old and maintained good health.

## EXAMINATION

On examination, the boy was moderately built and nourished. He had tonic and clonic movements of the upper limb and lower limb with uprolling of eyeball and froth in mouth at the time of admission. His convulsions were brought under control by the casualty medical officer.

He was drowsy after the attack of convulsion was brought under control. He was responding to painful stimulus by resisting it.

Anthropometric measurements included, height 126 cm (70th centile), weight 22 kg (50th centile). He was afebrile. His pulse was 110 per minute, and respiratory rate was 24 per minute. The blood pressure recorded was 90/70 mm Hg.

There was no pallor, no edema and no lymphadenopathy. There was tongue bite. Respiratory system revealed presence of crepitations at basal region. Abdominal examination revealed presence of mild distension. There was no hepatosplenomegaly.

The central nervous system examination revealed mental function normal. No cranial nerve was involved. No motor or sensory involvement. There were no meningeal signs.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 6,700 cells/cu mm
DLC	: P <sub>80</sub> L <sub>18</sub> E <sub>2</sub>
ESR	: 22 mm in 1st hour

Blood sugar	: 98 g/dL
Serum calcium	: 8 mg/dL
Chest X-ray	: Patchy pneumonitis
EEG	: Shows random spikes followed by slow waves
CT scan	: Normal

## DISCUSSION

An 8-year-old boy presented with tonic-clonic type of seizures without having any history suggestive of any infection associated with abnormal EEG findings will help come to the diagnosis of generalized tonic-clonic type of convulsion, i.e., epilepsy.

Seizures are common neurological disorder in pediatric age group. It occurs in 3–5% of children. A seizure or convulsion is defined as paroxysmal involuntary disturbance of brain function that may be manifested as an impairment or loss of consciousness, abnormal motor activity, behavioral abnormalities, sensory disturbances, or autoimmune dysfunction. Some seizures are characterized by abnormal movements without loss of impairment of consciousness.

Epilepsy is defined as recurrent seizures unrelated to fever or to an acute cerebral insult. The highest incidence of epilepsy is in the 1st year of life. It decreases after that age. The second peak is seen in second decade of life explaining the higher prevalence of epilepsy reported in adolescence. Generalized epilepsy accounts for most of the newly diagnosed cases in the first 5 years of life. After that, partial epilepsy account for 50% or more of newly identified epilepsies.

## CLASSIFICATION

Etiologically seizure disorders can be classified into two broad groups provoked seizures and unprovoked seizures. Provoked seizures occur in response to an insult to the central nervous system (e.g., infection, head injury) or in association with severe systemic insult (uremia, hypoglycemia).

### A. Partial seizures:

1. Simple partial (Consciousness retained)
  - ♦ Motor
  - ♦ Sensory
  - ♦ Autonomic
2. Complex partial (consciousness impaired)
3. Simple partial, followed by impaired consciousness
4. Consciousness impaired at onset
5. Partial seizures with secondary generalization

### B. Generalized seizures:

1. Absence
  - ♦ Typical
  - ♦ Atypical
2. Generalized tonic-clonic
  - ♦ Tonic
  - ♦ Clonic
  - ♦ Myoclonic
  - ♦ Atonic
  - ♦ Infantile spasm

## CLINICAL FEATURES (FIG. 1)

### Idiopathic Generalized Epilepsies

In 1989, The International League Against Epilepsy (ILAE) defined the criteria of idiopathic generalized epilepsies (IGEs) as follows—IGEs are forms of generalized epilepsies in which all seizures are initially generalized (absences, myoclonic jerks, and generalized tonic-clonic seizures), with an EEG impression that is a generalized, bilateral, synchronous symmetrical discharge.

The patient has a normal interictal state, without neurological or neuroradiological signs. In general, interictal EEGs show normal background activity and generalized discharges, such as spikes and polyspike-waves (>3 Hz). The discharges are increased by slow sleep. The various syndromes of IGEs differ mainly in age of onset.

Benign neonatal familial convulsions, benign neonatal convulsions and benign myoclonic epilepsy in infancy are the idiopathic generalized epilepsies. The onset either during the first few days of life or during 1st or 2nd year of life as the name indicates.

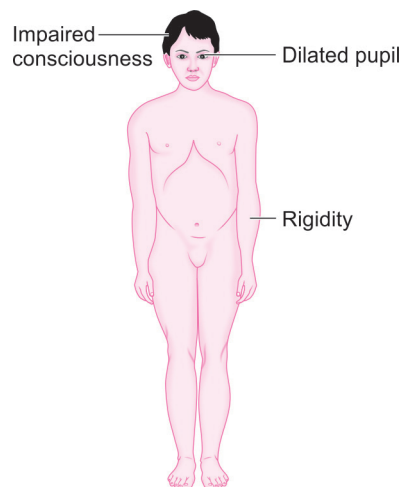


Fig. 1: Clinical features.



## GENERAL FEATURES

- Abnormal motor activity
- Behavioral abnormality
- Sensory abnormality
- Autoimmune dysfunction

### Partial Seizures

Partial seizures predominantly involve a focal area of brain and the presence of a focal epileptic abnormality in the interictal EEG is a strong evidence of a partial seizure disorder. These can be nonlesional or lesional epilepsies depending on whether an underlying anatomic abnormality related to the seizure activity is found on imaging procedure, preferably a magnetic resonance imaging. The nonlesional group includes benign childhood partial epilepsies while the lesional group includes various etiologies.

*Simple partial seizures:* The movements are characterized by asynchronous clonic or tonic movements. They tend to involve face, neck and extremities. Automatisms do not occur. But some patients complain of aura in the form of chest discomfort and headache. This may be the only manifestation of seizure. The distinguishing characteristics of simple partial seizures (SPS) involve, patients remain conscious and may talk during the seizure. No postictal phenomenon follows the event. EEG may show spikes or sharp waves unilaterally or bilaterally or a multifacial spike pattern.

*Complex partial seizures:* Complex partial seizures (CPS) may begin with a simple partial seizure with or without an aura followed by impaired consciousness. Onset may coincide with altered consciousness. The aura may comprise vague, unpleasant feelings, epigastric discomfort. The presence of aura always indicates a focal onset of seizure. There may be brief blink stare or a sudden cessation or a pause in activity that is frequently overlooked by parents. The period of altered consciousness may be brief and infrequent. Only an experienced observer or an EEG may be able to identify the event.

Automatisms are a common feature of CPS. It occurs in approximately 50–75% cases. The frequency of automatism is more in older children. Automatisms develop after the loss of consciousness and may persist into postictal state. But these are not recalled by child. The automatic behavior observed in infant is characterized by lip smacking, chewing, swallowing and excessive salivation.

Radiographic studies including CT scanning and especially MRI are most likely to identify an abnormality in temporal lobe of the child with CPS.

### Generalized Seizures

*Absence seizures:* Simple typical absence petit mal are characterized by a sudden cessation of motor activity or speech with blank facial expression and flickering of eyelids. These are uncommon before age of 5 years. It is more prevalent in girl. These are not associated with aura. They rarely persist longer than 30 seconds. They are not associated with postictal state. These features differentiate from complex partial seizures. EEG shows a typical 3/sec spike and generalized wave discharge.

*Generalized tonic-clonic seizures:* These are extremely common. It may follow partial seizure with the focal onset. They may be associated with aura. Patients suddenly lose consciousness, shrill piercing cry and rolling back eyeballs can occur. Entire body musculature undergoes tonic contractions. They rapidly became cyanotic and associated with apnea. The clonic phase of the seizure is heralded by rhythmic clonic contractions alternating with relaxation of all muscle groups. The clonic phase occurs towards the end of the seizure unusually lasts for few minutes. During the seizure child may bite their tongue. Loss of sphincter control particularly the bladder is common during generalized tonic-clonic seizures.

Neonatal seizures—poor myelination and incomplete dendrite arborization result in clinical seizures. Neonatal seizures may be subtle, multifocal clonic, focal clonic, generalized tonic and myoclonic events.

Subtle seizures may manifest as eye blinking, fluttering and buccolingual movements. The common causes are hypoxic ischemic encephalopathy, sepsis and bacterial meningitis. Metabolic seizures may be due to hypoglycemia, hypocalcemia, dyselectrolytemia and hypomagnesemia.

Myoclonic seizures—it is characterized by three important features—spasms, mental retardation and hypsarrhythmias. Spasms are abrupt contractions of less than 2 seconds in duration followed by sustained tonic contraction lasting for 2–10 seconds. Spasms can be flexor or extensor or both, typically occurring just before or on awakening or just before sleep. Hypsarrhythmia is the EEG feature in which all normal activity is replaced by asynchronous large amplitude slow waves mixed with multifocal spikes and sharp waves.

An underlying etiology is found in 85% (symptomatic group) which results from prenatal, perinatal or postnatal insults. In 10–15% the cause is not known (cryptogenic group) and this group carries a better prognosis. Areas of focal hypometabolism on positron emission tomography were reported with normal magnetic resonance imaging.

Juvenile myoclonic epilepsy—it is genetically inherited disorder with onset around the puberty. Bilateral symmetrical jerks of short duration involving mainly arms and shoulder are seen. Consciousness is not lost and most attacks occur on awakening. Generalized tonic-clonic or absence seizures may be associated. Sleep deprivation precipitates attacks. EEG shows bilateral multi spikes and wave pattern.

Lennox-Gastaut syndrome—Lennox-Gastaut syndrome (LGS) is characterized by three main characteristics:

1. A triad of seizure types—axial tonic spasms, atonic seizures and atypical absences.
2. EEG abnormalities consisting of diffuse slow (2–2.5 Hz) and spikewave discharges when awake, bursts of 10 Hz rhythms in sleep and generalized 3 Hz spikewave discharges (petit mal variant) on awakening.
3. *Slowing and plateauing of cognitive development*: LGS accounts for 3% of childhood epilepsy. Usually they are idiopathic or cryptogenic. Symptomatic cases (with definable etiology) are rare. LGS manifests in children aged 1–8 years. Onset can be with any one of the seizure types described but other seizure types such as myoclonic. Generalized tonic-clonic seizures (GTCS) or partial seizures are frequently associated with this syndrome. Seizure frequency is high and status epilepticus is frequent, and is seen in over two-thirds of cases. Carbamazepine is most effective for tonic seizures and sodium valproate for atypical absences. The effect of lamotrigine and *ethosuximide* is long-lasting. In occasional cases vigabatrin and *gabapentin* are effective.

#### ESSENTIAL DIAGNOSTIC POINTS

- Recurrent nonfebrile seizures
- Often, interictal electroencephalographic changes
- Classified as focal partial onset and generalized

## INVESTIGATION

Estimation of glucose, calcium and screening tests for neurometabolic causes usually suffice.

The interictal EEG is not always abnormal inpatients with epilepsy. The yield from routine EEG can be increased by repeating waking recording, recording during sleep and by using activating techniques—hyperventilation, photic stimulation and specific trigger in reflex epilepsies.

When the nature of attack is uncertain to determine the seizure type, videotelemetry EEG is used. EEG shows slow random spikes followed by slow waves in tonic, clonic type. In absence seizures a 3 per second spike and slow wave or multiple spike discharges are seen. Myoclonic is characterized by grossly chaotic record with very tall waves often exceeding 200 millivolts with the frequency of 1–2 per second. Absence of electrical activity suggests subdural hematoma.

Special electrodes—nasopharyngeal, anterior-temporal and sphenoidal electrodes can be used when routine EEG has not shown epileptiform discharges. Use of intracranial electrodes is indicated in patients with medically intractable epilepsy undergoing presurgical evaluation.

## Imaging in Epilepsy

MRI, CT scan, and functional imaging with single photon-emission computed tomography (SPECT) or positron emission tomography (PET) are used to evaluate the epileptic child. These are indicated in partial seizures, seizures with focal neurological deficits, dysmorphic features, and focal EEG abnormalities. Findings may include atrophies, inflammatory, malformations, neoplasia and vascular malformation.

Neuroimaging, either CT or MRI is necessary in all cases of partial epilepsy, neonatal onset seizures, seizure onset after 20 years of age, generalized seizures not responsive to therapy, and in the presence of focal neurological signs.

MRI is useful in defining etiology like small focal pathologies, migration disorders and malformation. MRI is preferred imaging modality for investigation of epilepsy. It can detect hippocampal sclerosis, neuronal migration disorders.

MRI is essential in intractable complex partial seizures with CT negative or unclear, seizures with focal neurological signs and CT negative or unclear and during presurgical evaluation. MRI is the preferred imaging modality for the investigation of epilepsy.

*Single photon-emission computed tomography*: The epileptic focus is imaged interictally in the region of reduced cerebral blood flow. A significant asymmetry of cerebral blood flow has been noted in about 50% of cases in temporal lobe epilepsy.

Due to poor sensitivity and specificity interictal SPECT studies have little role in routine investigation in pediatric procedure.

**Positron emission tomography:** It has a superior spatial resolution. Interictally, the epileptic focus is an area of reduced glucose metabolism. Partial seizures are associated with increase in both regional cerebral blood glucose metabolism and blood flow. The current role of SPECT and PET is useful when high quality MRI has not shown a relevant structural abnormality in patients who are the candidates for surgical treatment.

#### LABORATORY SALIENT FINDINGS

- Lumbar puncture: CSF analysis
- PCR for herpes
- CT scan
- MRI
- SPECT or PET scan
- Serum Ca, PO<sub>4</sub>, glucose, BUN, amino acid screen

#### TREATMENT

The decision to treat a child with an antiepileptic drug (AED) depends on the frequency of seizures, epilepsy syndrome and neurological findings. The decision to treat a single unprovoked seizure should be individualized. Numerous attempts have been made to predict accurately the risk of epilepsy developing after the first unprovoked seizure.

Treatment may not be recommended after a single brief generalized tonic-clonic seizure but necessary after a cluster of seizures or an episode of status epilepticus. A child with severe physical and learning difficulties who develops infrequent myoclonic or atypical absence (complex partial) seizures may not require AED but a child with normal intelligence, frequent absences and generalized tonic-clonic seizures on wakefulness may require treatment. Once and AED is started, the objective is to achieve complete seizure control without side effects and to use the most appropriate formulation for the child (Table 1).

The choice of AED and prognosis of epilepsy depend on the identification of the epileptic syndrome or seizure type (Table 2). Once the most appropriate AED has been selected, it should be used alone (monotherapy) and in the lowest dose that control the seizures without producing unacceptable side effects.

Neonates, infants and children under the age of 2 years frequently require higher doses than older children, because of a higher rate of drug metabolism. If initial seizure control is sub-optimal, the AED dosage should be increased

**TABLE 1:** Pediatric dosages of anticonvulsant drugs.

Drugs	Usual total daily dosage (mg/kg/day)	Doses/day
Acetazolamide	10–20	2
Carbamazepine	10–25	2/3
Clobazam	0.5–1.5	2
Clonazepam	0.1–0.3	2/3
Ethosuximide	15–35	2(3)
Gabapentin	15–30	3
Lamotrigine	0.5–3.0	2
Nitrazepam	0.5–1	2/3
Phenobarbitone	4–10	2
Phenytoin	4–15	2(1)
Sodium valproate	15–60	2
Vigabatrin	20–100	2

**TABLE 2:** Drugs of first, second and third choices in the treatment of various seizure types/epilepsies.

	First	Second	Third
<i>Primary generalized</i>			
Tonic-clonic	Sodium valproate	Lamotrigine	• Carbamazepine • Phenytoin
Myoclonic	Sodium valproate	Lamotrigine	• Clonazepam • Ethosuximide • Phenobarbitone
Tonic	Sodium valproate	Lamotrigine	• Phenytoin • Clobazam • Phenobarbitone
Absence	Sodium valproate	• Lamotrigine • Ethosuximide	Clobazam
Partial (simple/complex)	Carbamazepine	• Sodium valproate • Vigabatrin	• Lamotrigine • Gabapentin • Phenytoin • Clobazam • Acetazolamide
Infantile spasms	Vigabatrin	• Sodium valproate • Nitrazepam (ACTH)	Lamotrigine Prednisone

gradually until either seizure control is achieved or unacceptable side effects develop. If side effects occur before seizure control, the child will require substitution with a different drug or an additional AED (polytherapy).

If initial seizure control occurs with first AED, and next most appropriate AED and once complete seizure control is achieved, the first drug can be withdrawn after a seizure-free period of 2–3 months.

If the initial AED is wholly ineffective, the first drug should be replaced with second one simultaneously, maintaining monotherapy. Polytherapy with two AEDs may result in additional (even complete) seizure control in another 5–10% of children. But the problems of polytherapy are pharmacokinetic interactions potentially reducing the effectiveness of each drug, difficulty in interpreting the effect of each drug, cumulative toxicity and increased risk of idiosyncratic toxic interactions.

The currently recommended first-line drugs in treating majority of childhood epileptics are sodium valproate (VPA) and carbamazepine (CBZ). Most pediatric epilepsy syndromes are associated with generalized seizures and hence VPA is the drug of choice. Syndromes associated with partial seizures are less common and CBZ is the preferred AED. Though adrenocorticotrophic hormone (ACTH) has been used for the treatment of infantile spasms of West syndrome, vigabatrin or VP should be the drugs of first choice.

Phenytoin and phenobarbitone are useful only when the other drugs have failed and where seizure control is the major priority. The use of benzodiazepines is restricted by acute toxicity, development of tolerance or tachyphylaxis hence rarely, if ever, the initial AEDs.

## Stopping Antiepileptic Drug Treatment

As many as 70–80% of the patients on AED treatment will eventually become seizure free. Drug withdrawal can be considered after a patient has been seizure free for three or more years. The risk of relapse remission is about 20% overall.

Since the safety of drug withdrawal cannot be guaranteed in any one case, the relative risks of continued drug intake against the risk of further seizures inherent in drug withdrawal should be discussed. If a decision to withdraw medication is made, discontinuation of the treatment should be undertaken slowly, over a period of months, to minimize the risks of relapse.

## New Antiepileptic Drugs (Table 3)

Felbamate, which blocks N-methyl-D-aspartate (NMDA) receptor, is indicated for adjunctive treatment of partial seizures, generalized seizures, infantile spasms and Lennox-Gastaut syndrome. The initial recommended dose of felbamate as adjunctive therapy in children was 15–45 mg/kg/day.

Gabapentin, a  $\gamma$ -aminobutyric acid (GABA) analogue, is indicated for adjunctive treatment of partial and secondarily generalized seizures.

The optimal therapeutic dose of gabapentin in pediatric patients ranges from 30–90 mg/kg/day with higher doses being necessary for refractory partial epilepsy. A reduction rate of more than 50% in partial or generalized seizures was seen in 34.4% patients with 6.25% becoming seizure free in an open label, add on study of gabapentin.

Lamotrigine blocks voltage-dependent sodium channels (**Table 4**). Used as adjunctive therapy of partial seizures, it has a specific role in the treatment of Lennox-Gastaut syndrome. Effective maintenance doses in children are 1–15 mg/kg/day. Dosing is markedly influenced by concomitant therapy. Even monotherapy with lamotrigine is found to be effective. It has been shown to be effective to treat juvenile myoclonic epilepsy, infantile spasms.

Tiagabine selectively inhibits the reuptake of GABA into neurons and glia. It is indicated for adjunctive therapy of partial seizures or as monotherapy. Dosing in children should begin

**TABLE 3:** Seizure/epilepsy type.

Antiepileptic drug	Partial	Primary generalized	Infantile spasm	Lennox-Gastaut syndrome	Myoclonic	Absence
Felbamate	+	+	+	+	+	+
Gabapentin	+	+/-	-	-	-	-
Lamotrigine	+	+	?	+	+	+
Oxcarbazepine	+	+/-	-	-	-	-
Vigabatrin	+	+/-	+	+/-	-	+/-

(+: efficacious; -: no efficacy proven; +/-: mixed results among population; ?: needs further evaluation)

TABLE 4: Lamotrigine dose recommendations (mg/day) for children.

Concurrent AED	Weeks 1 and 2	Weeks 3 and 4	Usual maintenance dose
EIAED	2.0 mg/kg/day	5.0 mg/kg/day	5–15 mg/kg/day
Monotherapy	0.5 mg/kg/day	1.0 mg/kg/day	2–8 mg/kg/day
Valproic acid	0.2 mg/kg/day	0.5 mg/kg/day	1–5 mg/kg/day

(EIAED: enzyme-inducing antiepileptic drug; AED: antiepileptic drug)

with 0.1 mg/kg/day for first 2 weeks and increased by 0.1 mg/kg/day every 2 weeks until an optimal effect is reached. The most common adverse events are somnolence, dizziness and headache.

Topiramate is useful both as monotherapy and adjunctive drug in the treatment of Lennox-Gastaut syndrome, infantile spasms and refractory partial seizures. It acts by three mechanisms, i.e., blocking the voltage-dependent sodium channels, potentiation of GABA-mediated effects and antagonism of excitatory glutamate receptors. The initial dose is 1 mg/kg/day with target maintenance doses of 3–6 mg/kg/day and can even be increased up to 10 mg/kg/day according to the need. The side effects include somnolence, fatigue, abnormal thinking, headache, diplopia, ataxia, psychomotor slowing, speech difficulty, paresthesia, impaired concentration and confusion. Weight loss and nephrolithiasis are the other side effects.

Vigabatrin is a specific, reversible GABA aminotransaminase inhibitor. In children, it has been proved to be safe and efficacious in the treatment of partial seizures, generalized seizures and in some patients with Lennox-Gastaut syndrome. It is particularly useful in the treatment of infantile spasms. Vigabatrin is the drug of choice especially in symptomatic cases with tuberous sclerosis. Fifty percent respond in a few days. Steroids (ACTH or prednisolone) are tried for non-responders or relapsing cases. Sodium valproate and benzodiazepines also control infantile spasms in 50–60% of cases.

Epilepsy Surgery

Epilepsy surgery is becoming an increasingly used therapy for young children and infants with severe, medically intractable seizures. The most commonly performed surgery in older children is temporal lobe resection while nontemporal lobe resections, corpus callosotomies and hemispherectomies are more commonly performed in younger children. Surgery should be considered early in the course of the catastrophic seizure disorders of childhood-infantile spasms such as Sturge-Weber syndrome and Rasmussen’s encephalitis.

PROGNOSIS

The idiopathic epilepsies with partial seizures (rolandic epilepsy, partial childhood epilepsy with occipital paroxysms) have a good prognosis for spontaneous remission and for control with medication. The prognosis for remission for childhood absence epilepsies is about 80% with appropriate therapy. Control is poor with juvenile absence epilepsies. The remission rate for juvenile myoclonic epilepsy is 70–80% with continued therapy. However after discontinuation of the medication, seizures recur in about 70% of the patients.

The incidence of intractable seizures is high with symptomatic epilepsies with static or progressive disorders. Symptomatic West syndrome has a bad prognosis while cryptogenic form has a favorable prognosis. Similarly the prognosis of Lennox-Gastaut syndrome varies according to whether it has a cryptogenic or symptomatic background. In Landau Kleffner syndrome though the prognosis for disappearance of seizures is favorable, the prognosis for aphasia is poor. The prognosis for reflex epilepsies is good both with appropriate AED therapy and avoidance of the specific precipitating stimuli. Febrile seizures are age limited and improvement occurs with time.

STATUS EPILEPTICUS

Status epilepticus is defined as two or more seizures without regaining consciousness in between or a continuous seizure lasting for more than 5 minutes. Physiologically status epilepticus is defined as recurrent seizures without complete normalization of neurochemical and physical homeostasis in the brain between seizures. Children with prior neurological abnormalities are more susceptible.

The etiology of status epilepticus varies. Status epilepticus can occur in the setting of an acute illness, in patients with established epilepsy or for the first time as unprovoked seizures.

Remote symptomatic, acute symptomatic and febrile seizures are the major causes of status epilepticus in children while the cause for status is



unknown in 24–39% of the children. Progressive encephalopathy is the cause in 2–6% of the cases. Overall mortality varies from 3 to 10% with almost all fatalities associated with acute central nervous system insults or progressive neurologic disorders.

Neurologic sequelae in children with idiopathic or febrile status is rare. Neurologically normal children with status epilepticus as their first unprovoked seizure have the same risk of experiencing subsequent seizures of any type as children who present with a brief first seizure.

The risk of recurrent episodes of convulsive status is 50% in neurologically abnormal children but very low in normal children. The favorable outcome of status epilepticus in children may be related to the therapy and the resistance of the immature brain to damage from seizures.

## Management of Status Epilepticus

The goals in the management of status epilepticus includes, to stop seizure activity as quickly as possible to protect the neuron from seizure induced damage and to allow for full recovery from the episode of status epilepticus.

The general measures include stabilization of airway, with adequate respiratory support, maintenance of blood pressure. Then the blood sample should be collected for evaluation of hematological and serum chemistry parameters and determination of AED levels.

Plasma glucose should be determined and glucose should be given only in the presence of documented hypoglycemia. Hyperpyrexia should be corrected. Status-induced transient acidosis should not be corrected as the pH rapidly normalizes once status epilepticus is controlled. Supplement oxygen may be helpful.

## Emergency Drug Treatment

### *Premonitory Stage*

Diazepam 0.25–0.5 mg/kg IV or 0.5–0.75 mg/kg rectally, repeated once 15 minutes later if status continues to threaten or lorazepam 0.1 mg/kg IV bolus if seizures continue or status develops.

### *Stage of Early Status*

Lorazepam 0.1 mg/kg IV bolus (if not given earlier) is given if status continues after 30 minutes.

### *Stage of Established Status*

Phenobarbital IV infusion of 15–20 mg/kg at a rate of less than 100 mg/min or phenytoin IV infusion of 20 mg/kg at a rate of less than 25 mg/min if status continues after 30–60 minutes.

### *Stage of Refractory Status*

General anesthesia with either Propranolol 2 mg/kg IV bolus, repeated if necessary, and then followed by a continuous infusion of 5–10 mg/kg/h, initially to 1–3 mg/kg/h when seizures have been controlled for 12 hours, the drug dosages should be slowly tapered over 12 hours or thiopental 100–250 mg IV bolus given over 20 seconds, with further 50 mg boluses every 2–3 minutes until seizures are controlled, followed by a continuous IV infusion to maintain a burst suppression pattern on the EEG (usually 3–5 mg/kg/h). Thiopental should be slowly withdrawn 12 hours after the last seizure.

#### CAUSES OF REFRACTORY EPILEPSY

- Inadequate serum level of drug
- Drug toxicity—phenytoin
- Metabolic—inborn errors
- Incorrect identification
- Paradoxical reaction of medications

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# Febrile Convulsions

## PRESENTING COMPLAINTS

A 10-month-old girl was brought with the complaints of:

- Cough and cold since 3 days
- Fever since 2 days
- Irritable since 1 day
- Abnormal movements and uprolling of eyeball since 20 minutes

## History of Presenting Complaints

A 10-month-old girl was brought to the casualty with history of convulsions. Convulsion was generalized. It involved both upper and lower limbs. It was tonic and clonic type with uprolling of eyeball. According to the mother the convulsions lasted for 5 minutes. By the time child came to hospital, there was no convulsions. But the child was irritable. Mother also told that her daughter was getting treatment for cough, cold, and fever since 2 days by the family doctor.

### CASE AT A GLANCE

#### Basic Findings

Length	: 72 cm (75th centile)
Weight	: 8.5 kg (75th centile)
Temperature	: 39°C
Pulse rate	: 130 per minute
Respiratory rate	: 32 per minute
Blood pressure	: 60/40 mm Hg

#### Positive Findings

##### History

- Convulsions
- Fever
- Cough and cold

##### Examination

- Irritable child
- Febrile
- Convulsions

##### Investigation

- Anemia
- TLC: 16,000 cells/cu mm
- CSF: Normal
- CT scan: Normal

## Past History of the Patient

She was the first sibling of nonconsanguineous marriage. She was born at full term by normal delivery. Her birth weight was 3 kg. There was no significant postnatal event. Child started to take the breastfeeds immediately. She was on breast milk exclusively for 3 months. Weaning was started as per the advice of the family doctor from 4th month onwards. Developmental milestones were normal. There was no family history of convulsions. There was no history of similar illness.

## EXAMINATION

On examination, the child was moderately built and moderately nourished. She was alert, irritable and was crying. Anthropometric measurements included, the length of the child was 72 cm (75th centile), the weight was 8.5 kg (75th centile). The head circumference was 42 cm.

The child was febrile, i.e., 39°C. The pulse rate was 130 per minute, the respiratory rate was 32 per minute. The blood pressure recorded was 60/40 mm Hg. There was pallor, no lymphadenopathy, no edema, and no cyanosis.

There were signs of rhinitis. Throat examination was normal. Respiratory system revealed presence of crepitations at base of the lung. All other systemic examinations were normal. Pupils were round, reactive and dilated. There was no involvement of motor and sensory systems. There was no cranial nerve involvement.

## INVESTIGATION

Hemoglobin	: 9 g/dL
TLC	: 16,000 cells/cu mm
DLC	: P <sub>80</sub> L <sub>18</sub> M <sub>2</sub>
ESR	: 18 mm at the 1st hour
CSF	: Normal
CT scan	: Normal

## DISCUSSION

The child had convulsions lasting for 5 minutes. The convulsions are of generalized, clonic and

tonic type. At the time of convulsion, the child had fever as a result of upper respiratory tract infection. There was no loss of consciousness and postictal drowsiness. As the central nervous system examination and CT scan was normal, the diagnosis of febrile convulsion was made.

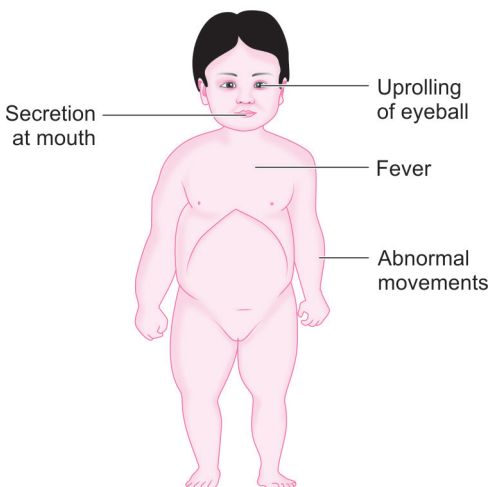
Febrile seizures are seizures that occur between the age of 6 months and 6 years with a temperature of 38°C (100.4°F) or higher, that are not the result of central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures.

A simple febrile seizure is a primarily generalized, usually tonic-clonic, attack associated with fever, lasting for a maximum of 15 minutes, and not recurrent within 24-hour period. A complex febrile seizure is more prolonged (>15 minutes), is focal, and/or reoccurs within 24 hours. Febrile status epilepticus is a febrile seizure lasting longer than 30 minutes. Some use the term simple febrile seizure plus for those with recurrent febrile seizures within 24 hours. Most patients with simple febrile seizures have a very short postictal state and usually return to their baseline normal behavior and consciousness within minutes of the seizure.

But it is frequent if the temperature rises abruptly. There are two types of febrile convulsions: one is simple typical febrile convulsion, and second is atypical febrile convulsions.

### CLINICAL FEATURES (FIG. 1)

By definition, febrile seizures occur between the ages of 6 months and 6 years. Although there are



**Fig. 1:** Clinical features.

exceptions, children of ages that fall outside this range are less likely to have febrile seizures.

A high incidence of epilepsy has been reported in children over 6 years of age with febrile seizures and these seizures have been called epileptic seizures precipitated by fever. These children have other risk factors for the development of epilepsy.

The most commonly associated illnesses are upper respiratory infections, gastrointestinal infections, otitis media and roseola. A viral infection is implicated in more than 80% of cases. The primary human herpes virus types 6 and 7 have recently been implicated as possible specific causal agents. A bacterial pathogen was suspected of children with febrile seizures. Shigellosis is a bacterial gastrointestinal infection associated with febrile seizures.

### Simple versus Complex Febrile Seizures

The idea of separating febrile seizures into simple and complex subgroups originated from the description of clinical risk factors that predicted a much higher probability of chronic epilepsy according to seizure subtype. The risk factors includes:

- Seizure during greater than 15 minutes
- Focal seizure manifestation
- More than one seizure in 24 hours
- Abnormal neurologic status
- Afebrile seizure in a parent or sibling

Simple febrile seizures occur within 24 hours of the onset of the temperature. These seizures usually lasts for about less than 10 minutes. The convulsions are generalized type. But more than one episode may occur. There are no postictal neurological deficits. There may be family history of febrile convulsions. Electroencephalogram (EEG) will be normal. There may be no further seizures. About 3–10% of the children may develop recurrent seizures. These are commonly seen between the age of 6 months and 6 years.

At least 80% of febrile seizures are generalized and simple. However, a febrile seizure can be of partial or different generalized type. In addition, tonic, clonic and even atonic episodes may characterize febrile seizures. Some children have multiple seizures within a 24 hours period. Prolonged seizures have been reported in children. One-half of these seizures lasted more than 30 minutes. Febrile status epilepticus occurs more commonly in girls with focal seizures.

Convulsions due to organic neurological damage are precipitated with fever as the cerebral threshold for the seizure is reduced with the

elevation of the temperature. Infections of central nervous system are important causes of convulsion associated with fever. Atypical febrile convulsions include unilateral seizure, multiple convulsions in the same febrile illness, Todd's paralysis and status epilepticus.

When complex febrile seizures occur, the risk of epilepsy increases to 50% when all risk factors are present. The exact mode of inheritance of febrile seizures is uncertain. A positive family history can be elicited in 25–40% of children. Some studies show high concordance rate in monozygotic versus dizygotic twins. In a large family with multiple affected individuals, linkage has been made to a locus on chromosome 8q13-21.

A third of children with febrile seizures experience a second episode. The most important identified risk factor is the age of onset. Studies have confirmed that 50% of children younger than 1 year of age experienced a recurrence. Additional risk factors include a history of febrile seizures in a first-degree, seizures induced by low-grade fever and a brief duration between the onset of fever and the convulsion.

The greatest concern for the family following their child's febrile seizure is the risk of developing epilepsy, which is defined as two unprovoked seizures. Presence of family history of epilepsy, neurodevelopmental retardation and atypical episode of attacks increases, the recurrent risk of febrile episodes and subsequent epilepsy. Three risk factors for unprovoked seizures were identified in this study.

1. Abnormal neurologic examination prior to the first febrile seizure
2. A history of afebrile seizure in a parent or sibling
3. A complex first febrile seizure

The risk of developing into epilepsy in febrile convulsions is more if the attack has lasted for more than 30 minutes, if the convulsion is focal or if there are abnormal EEG findings.

**ESSENTIAL DIAGNOSTIC POINTS**

- Fever
- Abnormal movements of limbs and body
- Child is unconscious
- No postictal residuals
- More common between 6 months and 6 years

**GENERAL FEATURES**

- Fever
- Generalized convulsion
- Common between 6 months and 6 years

**DIAGNOSIS**

**Electroencephalogram**

In many case if an EEG is indicated, it is delayed until or repeated after more than 2 weeks have passed. An EEG should, therefore, generally be restricted to special cases in which epilepsy is highly suspected, and, generally, it should be used to delineate the type of epilepsy rather than to predict its occurrence. If an EEG is done, it should be performed for at least 20 minutes in wakefulness and in sleep according to international guide lines to avoid misinterpretation and drawing of erroneous conclusions.

At times, if the patient does not recover immediately from a seizure, then an EEG can help distinguish between ongoing seizure activity and prolonged postictal period, sometimes termed a nonepileptic twilight state. EEG can also be helpful in patients who present with febrile status epilepticus because the presence of focal slowing pattern present on the EEG obtained within 72 hours of the status has been shown to be highly associated with magnetic resonance imaging (MRI) evidence of acute hippocampal injury.

**Blood Studies**

Blood studies (serum electrolytes, calcium, phosphorus, magnesium and complete blood count) are not routinely recommended in the work-up of a child with a first simple febrile seizure. Blood glucose should be determined in children with prolonged postictal obtundation or with poor oral intake (prolonged fasting).

Serum electrolyte values may be abnormal in children after a febrile seizure, but this should be suggested by precipitating or predisposing conditions elicited in the history and reflected in abnormalities of the physical examination. If clinically indicated (e.g., in a history or physical examination suggestive of dehydration), these tests should be performed. A low sodium level is associated with higher risk of recurrence of the febrile seizure within the following 24 hours.

Lumbar puncture should be done for cerebrospinal fluid (CSF) analysis. This may help to diagnose intracranial infection. Lumbar puncture should be performed in children under the age of 18 months with the first attack of febrile convulsions.

The most important aspect of diagnosis is to rule out an underlying infection of the central nervous system. Seizures associated with meningitis are usually brief generalized tonic-clonic seizures similar simple febrile seizures.

**LABORATORY SALIENT FINDINGS**

- Evaluation underlying cause of fever
- EEG
- CT scan
- MRI
- *Lumbar puncture:* CSF analysis

**TREATMENT****Temperature Control**

Because the majority of febrile seizures are simple, the physician will assess the child in the postictal state to determine the etiology of the fever. The initial step should be to measure the temperature and if the child is still febrile to lower it in an effort to avoid recurrences. The acetaminophen (15 mg/kg/dose) should be given every 4–6 hours when rectal temperature exceeds 37.9°C, if the child is vomiting, acetaminophen may be given rectally. Anti-inflammatory drugs can also be used.

In a prospective study, which compared to the efficacy of acetaminophen syrup (10 mg/kg/dose) with that of ibuprofen syrup (5 mg/kg/dose), children treated with ibuprofen had a significantly greater seizure reduction.

**Treatment of Acute Attack**

The drug of choice is diazepam, which can be given parenterally at doses of 0.5–1 mg/kg. its short half-life is preferable to the prolonged effects of parenteral phenobarbital. In cases where febrile seizures recur frequently, it is appropriate to provide the rectal diazepam to shorten the duration of seizures.

This condition should be managed by prompt reduction of temperature. The intravenous line should be started to maintain hydration and to give anticonvulsant medications. Injection of diazepam (0.2–0.3 mg/kg dose) slow intravenous with the maximum dose of 5 mg/dose is given to control convulsions. Phenobarbitone can be given in the dose of 20 mg/kg. When given intravenously action starts in 5–10 minutes, but the peak concentration in brain is reached in 30–60 minutes. Paraldehyde can be tried per rectally. It is diluted with olive oil when given per rectally.

If the seizure lasts for longer than 5 minutes, acute treatment with diazepam, lorazepam, or midazolam is needed. Rectal diazepam is often prescribed to be given at the time of recurrence of a febrile seizures lasting longer than 5 minutes.

Alternatively, buccal or intranasal midazolam may be used and is often preferred by parents. Intravenous benzodiazepines, phenobarbital,

phenytoin, or valproate may be needed in the case of febrile status epilepticus. If the parents are very anxious concerning their child's seizures, intermittent oral diazepam (0.3 mg/kg every 8 hours during fever) or intermittent rectal diazepam 0.5 mg/kg, administered as a rectal suppository every 8 hours), can be given during febrile illnesses. Intermittent oral nitrazepam, clobazam, and clonazepam (0.1 mg/kg/day) have also been used. Such therapies help to reduce, but do not eliminate, the risks of recurrence of febrile seizures.

Other therapies have included continuous phenobarbital (4–5 mg/kg/day in one or two divided doses), and continuous valproate 20–30 mg/kg/day in two or three divided doses). In the vast majority of cases, it is not justified to use continuous therapy owing to the risk of side effects and lack of demonstrated long-term benefits, even if the recurrence rate of febrile seizures is expected to be decreased by these drugs.

Antipyretics can decrease the discomfort of the child but do not reduce the risk of having a recurrent febrile seizure, probably because the seizure often occurs as the temperature is rising or falling. Chronic antiepileptic therapy may be considered for children with a high risk for later epilepsy. Currently available data indicate that the possibility of future epilepsy does not change with or without antiepileptic therapy. Iron deficiency is associated with an increased risk of febrile seizures, and thus screening for that problem and treating it appears appropriate.

**Prophylaxis**

Recurrence risk is 12% if there are no risk factors. It is 75–100% if there are risk factors. The risk factor includes disadvantages of social environment, seizure disorder of any type in first degree relative, onset before the age of 15 months, complex febrile seizures and suboptimal neurodevelopment. Prophylaxis is indicated in children with one or more risk factors. Three groups of anticonvulsants may be effective in preventing febrile seizures: barbiturates, benzodiazepines and valproic acid.

**Phenobarbital**

Until recently phenobarbital was considered the drug of choice for the prophylaxis of febrile seizures. When therapeutic levels of the drugs were maintained, it led to a significant reduction in the risk of recurrence. However, phenobarbital is poorly tolerated and compliance is problematic. Daily administration of phenobarbital results in



hyperkinesis, moodiness, irritability, sleep disturbances and decreased intelligence.

### Benzodiazepines

As a result of their pharmacokinetic properties, benzodiazepines can be effective when used to prevent febrile seizures intermittently. They are rapidly absorbed and have a short, effective half-life. Both oral diazepam and nitrazepam have been effective in preventing febrile seizure recurrences compared to placebo, even in children at high risk for febrile seizures. However, side effects, such as ataxia, somnolence, agitation, irritability and lethargy, should be expected.

### Valproic Acid

Valproic acid has been reported to be effective against febrile seizures. Because of the risk of serious side effects such as liver failure in young children, valproic acid is not recommended as preventive therapy for febrile seizures. However, in children with mixed febrile and afebrile seizures and children with a clear underlying epileptic syndrome, valproic acid is the drug of choice.

Continuous prophylaxis is advised in child with central nervous system disease, recurrent atypical seizures, and family history of epilepsy. The drugs used are sodium valproate—10–20 mg/kg/day or phenobarbitone 3–5 mg/kg/day. The duration of therapy is 1–2 years or 6 years of age whichever comes earlier. Carbamazepine and phenytoin are ineffective.

### Parent Education

Control of fever with antipyretic treatment may limit recurrences and although initial temperature rise can be missed, the same applies for intermittent benzodiazepine treatment. The bottom

line is that parents must feel comfortable with the final decision and a treatment should not be imposed. There is no evidence that preventing new febrile seizures is associated with a more favourable prognosis than shortening the duration of seizures.

### CONCLUSION

Febrile seizures are a frequent and benign disorder. In more than 80% of children, they represent the expression of a genetically inherited response to fever. For these children, no treatment is required and parents should be reassured. Rarely, febrile seizures represent early evidence for later epilepsy.

The majority of children with risk factors for later epilepsy do not develop recurrent unprovoked seizures. Electroencephalography is not predictive of later epilepsy in children with febrile seizures. Benzodiazepines can be used to shorten the duration of febrile seizures, particularly if families live in remote areas and do not have access to immediate care. Only very rarely should daily prophylactic anticonvulsant therapy be considered for use in children with febrile seizures.

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# Guillain-Barré Syndrome

## PRESENTING COMPLAINTS

A 12-year-old boy was brought with the complaints of:

- Headache since 1 week
- Vomiting since 2 days
- Unable to walk and move the lower limbs since 1 day

## History of Presenting Complaints

A 12-year-old boy was brought to the hospital with history of headache and vomiting. Headache was diffuse and stabbing in nature. Headache never used to be relieved by analgesics. It was associated with vomiting. Vomiting was insidious in nature. There was also history of pain in lower back and in the arms. His mother had noticed that her son was having difficulty in walking. The boy was finding it very difficult to move his lower limbs. Boy complained that he was feeling pins and needles in the legs. 2 weeks back child had cough, cold and fever. This was treated by his family doctor.

## Past History of the Patient

He was the eldest sibling of consanguineous marriage. The boy was born at full term by normal

delivery. His birth weight was 3 kg. He was on breastfeeds immediately after the delivery. There were no significant postnatal events. His developmental milestones were normal. His performance at school was good.

## EXAMINATION

On examination, the boy was moderately built and moderately nourished. Anthropometric measurements included, his height was 138 cm (40th centile) and his weight was 36 kg (50th centile).

He was febrile. The pulse rate was 96 per minute, the respiratory rate was 20 per minute. The blood pressure recorded was 90/70 mm Hg. There was no pallor, no lymphadenopathy, no cyanosis, and no clubbing.

There was considerable weakness in the lower limbs. There was gross motor weakness in the legs. But there was no wasting. Generalized hypotonia was present. No tendon reflexes could be elicited. The left arm was also involved and he was unable to lift the spoon. His condition involved the trunk muscles and arms leading to complete paraplegia. Bilateral facial weakness was present. The boy even developed difficulty in swallowing. Hence, the nasogastric tube was given. Later he required mechanical ventilation.

## CASE AT A GLANCE

### Basic Findings

Height	: 138 cm (40th centile)
Weight	: 36 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 96 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 90/70 mm Hg

### Positive Findings

#### History

- Headache
- Vomiting
- Difficulty in walking
- Pain in the back

#### Examination

- Hypotonia
- Gross motor weakness in legs
- Gradual deterioration

#### Investigation

- CSF examination: Moderate increase in protein and pleocytosis

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 9,600 cells/cu mm
DLC	: $P_{70} L_{25} M_0 E_4 B_1$
ESR	: 30 mm in the 1st hour
Mantoux test	: Negative
CSF examination	: Moderate increase in protein (60 mg/dL) Pleocytosis (50–100 cells/cu mm)
CT scan	: Normal

## DISCUSSION

The boy developed paresthesia in both lower limbs and in the left arm after a viral infection. Gradually,

it made him unable to walk around as a result of muscle weakness and hypotonia. Later, it involved all the limbs producing quadriplegia. There is also involvement of the trunk muscles producing respiratory distress.

The Guillain-Barré syndrome is an acute, monophasic demyelinating neuropathy in which abnormal immune responses are directed against peripheral nerves. There will be an antecedent viral infection 2 weeks before the onset of weakness. It usually follows a viral infection such as infectious mononucleosis, mumps, measles, echovirus, coxsackie and influenza. Respiratory tract infections are most common and the remainders are mainly gastrointestinal infections. Enteritis caused by specific strains of *Campylobacter jejuni* is the inciting disease.

The basic myelin protein is altered and rendered immunogenic by the infection. These immune mechanisms may cause demyelination. *Campylobacter* infection has been strongly associated with severe forms and acute motor axonal neuropathy (AMAN) syndrome. Other subtypes include; acute inflammatory demyelinating polyneuropathy (AIDP); acute motor and sensory axonal neuropathy (AMSAN); and Miller-Fisher syndrome (MFS).

#### ESSENTIAL DIAGNOSTIC POINTS

- *Delayed hypersensitivity*: T cell-mediated antigen-glycoside antibodies
- Nonspecific respiratory and gastrointestinal symptoms
- Symmetric weakness of lower limbs, trunk, and face
- *Ataxia, ophthalmoplegia and cranial nerves*: IX, XI, III, VI

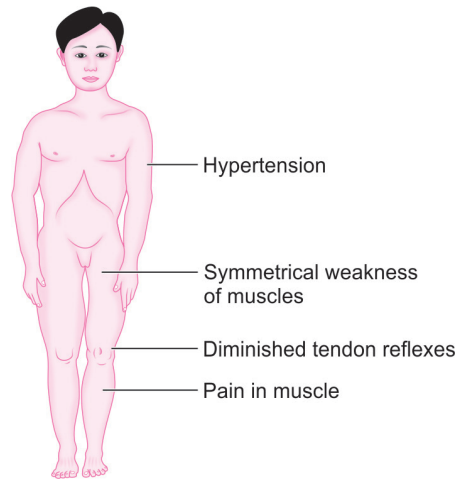
## **PATHOLOGY**

The pathologic findings are characterized by a marked segmental demyelination. In some cases, there is an early antibody attack on myelin, whereas in others, the process is mainly inflammatory. Both process lead to a macrophage response that causes myelin destruction.

It is characterized by symmetric weakness of the muscle, diminished reflexes and sensory involvement, i.e., usually paresthesia. Neurological manifestations usually begin after the viral illness that has already subsided. It is probably because peripheral lymphocytes are sensitized to a protein component of the myelin. These migrate into the peripheral nerve and cause myelin breakdown.

## **CLINICAL FEATURES (FIG. 1)**

Guillain-Barré syndrome is an autoimmune disorder often considered a postinfectious polyneuropathy



**Fig. 1:** Clinical features.

involving mainly motor but also sensory and sometimes autonomic nerves.

The paralysis usually follows a nonspecific gastrointestinal or respiratory infection by approximately 10 days. The original infection might have caused only gastrointestinal (especially *Campylobacter jejuni*, but also *Helicobacter pylori*) or respiratory tract (especially *Mycoplasma pneumoniae*) symptoms. Consumption of undercooked poultry, unpasteurized milk, and contaminated water are the main sources of gastrointestinal infections. Guillain-Barré syndrome is reported following administration of vaccines against rabies, influenza, and poliomyelitis (oral) and following administration of conjugated meningococcal vaccine, particularly serogroup C. Additional infectious precursors of Guillain-Barré syndrome include mononucleosis, Lyme disease, cytomegalovirus, and *Haemophilus influenzae* (for the Miller-Fisher syndrome).

The onset is gradual and progresses over days or weeks, the process plateaus in 1–28 days. Particularly in cases with an abrupt onset, tenderness on palpation and pain in muscles are common in the initial stages. Affected children are irritable. Weakness can progress to inability or refusal to walk and later to flaccid tetraplegia. Maximal severity of weakness is usually reached by 4 weeks after onset.

Initial symptoms include numbness and paresthesia, followed by weakness. There may be associated neck, back, buttock, and leg pain. Weakness usually begins in the lower extremities and progressively involves the trunk, the upper limbs, and, finally, the bulbar muscles, a pattern known as Landry ascending paralysis. Proximal and distal muscles are involved relatively symmetrically, but asymmetry is found 9% of patients.

Characteristically, it is symmetric, although minor differences between the sides are not rare. In about 50% of patients, the weakness is mostly distal, whereas in about 15% the proximal muscles are more extensively involved.

Paresthesias occur in some cases. Cranial nerve palsies can appear at any time during the illness. The facial nerve is involved most commonly. Oculomotor and other cranial nerve involvement is also seen occasionally.

Urinary retention or incontinence is a complication in about 20% of cases. Tendon reflexes are diminished or absent usually early in the course, but are sometimes preserved until later, and this finding may be misleading in arriving at an early diagnosis.

Respiratory paralysis occurs in 20–30% of children with Guillain-Barré syndrome. If the patients' respiratory function can be supported during the critical time of profound paralysis, complete recovery can be expected. Paralysis of the respiratory muscles is a common complication in severely involved patients, but even in the absence of respiratory symptoms vital capacity can be impaired.

The autonomic nervous system may also be involved in some cases. Profuse sweating, hypertension, postural hypotension, cardiac arrhythmias and gastrointestinal dysfunctions are manifestations of the autonomic dysfunction.

There is associated facial weakness and sometimes bulbar palsy may occur. It may occur at any age after 6 months. But it is commonly seen between the age group of 5 years and 9 years.

Distal sensory loss may be detectable and sensory ataxia can occasionally dominate the picture. Tendon reflexes are absent. Occasionally, extensor plantar responses are found. Headache, neck pain, back pain and limb pain are common in acute phase.

The variant of Guillain-Barré syndrome is characterized by external ophthalmoplegia, ataxia and areflexia. Bilateral facial paresis and internal ophthalmoplegia are other manifestations. Symptoms remain severe for 1–2 weeks before recovery starts. Recovery is generally complete. At present, it is a matter of dispute whether it should be distinguished from brainstem encephalitis.

The clinical course is usually benign and spontaneous recovery begins within 2–3 weeks. Most patients regain full muscular strength, although some are left with residual weakness. The tendon reflexes are usually the last function to recover. The improvement usually follows a gradient inverse to the direction of involvement, with recovery of bulbar function first and lower extremities weakness resolving last.

## DIAGNOSIS

Cerebrospinal fluid (CSF) study is essential for diagnosis. An elevation in the CSF protein content is characteristic. This exceeds 45 mg/dL in 88% of affected children and rises to its maximum by 4–5 weeks, thereafter gradually returning to normal. The CSF cell count is usually normal. Fewer than 10 leukocytes per cubic millimeter may be found. Significant pleocytosis (100+ cells/cu mm) occurs in about 5% of patients. They disappear rapidly for CSF, CSF glucose is normal. The results of bacterial culture are negative and viral culture rarely isolates specific viruses.

Motor nerve conduction velocities are greatly reduced, and sensory nerve conduction time is often slow. Electromyography shows evidence of acute denervation of muscle. Serum creatine kinase level may be mildly elevated or normal. Antiganglioside antibodies, mainly against GM<sub>1</sub> and GD<sub>1a</sub>, are sometimes elevated in the serum in Guillain-Barré syndrome, particularly in cases with primarily axonal rather than demyelinating neuropathy, and suggest that they might play a role in disease propagation and/or recovery in some cases. Muscle biopsy is not usually required for diagnosis; specimens appear normal in early stages and show evidence of denervation atrophy in chronic stages. Sural nerve biopsy tissue shows segmental demyelination, focal inflammation, and Wallerian degeneration but also is usually not required for diagnosis.

Serologic testing for *Campylobacter* and *Helicobacter* infection helps establish the cause if results are positive but does not alter the course of treatment, results of stool cultures are rarely positive.

Spiral MRI scanning is indicated if the clinical picture suggests the possibility of spinal cause for acute flaccid weakness, e.g., spinal angioma, hydromyelia, spinal trauma, epidural abscess or spinal tumor.

### GENERAL FEATURES

- Diminished reflexes
- Paresthesia
- Facial cranial nerve involvement
- Autonomus nervous system is involved
- Postural hypotension

### LABORATORY SALIENT FINDINGS

- *CSF analysis:* Cytoalbuminologic dissociation, high protein, normal glucose, IgG may be raised
- Nerve conduction velocities markedly decreased
- *Search for the cause:* Infection intoxication, autoimmune disease
- Electromyogram
- Spiral nerve biopsy

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes poliomyelitis, polymyositis, transverse myelitis and cerebellar ataxia. Acute dermatitis causes diagnostic confusion. But the doubt is clarified by creatine phosphokinase (CPK) enzymes. The toxicology screening should be done for lead, arsenic, thallium and mercury.

## TREATMENT

Treatment of Guillain-Barré syndrome is mainly symptomatic. The potential paralysis of the respiratory muscles should be considered in each patient, the facilities for tracheostomy and mechanical respiration should be readily available.

Chronic and intermittent forms of polyneuritis appear to show a clear-cut response to steroids. High dose pulsed methylprednisolone given intravenously is successful in some cases.

Natural course of the disease is self-limited. There will be gradual recovery in majority of the patients. In some patients, there will be severe paralyzes at onset. It may be associated with respiratory muscle involvement. These patients definitely require treatment. Supportive therapy includes assisted ventilation. Tracheostomy should be done if necessary.

Patients in early stages of this acute disease should be admitted to the hospital for observation because the ascending paralysis can rapidly involve respiratory muscles during the next 24 hours. Respiratory effort (negative inspiratory force, spirometry) must be monitored to prevent respiratory failure and respiratory arrest. Patients with slow progression might simply be observed for stabilization and spontaneous emission without treatment.

Rapidly progressive ascending paralysis is treated with intravenous immunoglobulin (IVIG), administered for 2, 3, or 5 days. A commonly recommended protocol of IVIG is 0.4 g/kg/day for 5 consecutive days, but some studies suggest that larger doses are more effective (1 g/kg/day for 2 consecutive days) and related to improved outcome. A good response is seen with intravenous immunoglobulin administered in the dose of 200–300 mg/kg/day for 5–10 days. Response is good if the treatment is given within 3–4 days. Recovery is complete, but takes about 6 months to 2 years for restoration of full function.

Plasmapheresis and intravenous immunoglobulin have also been recommended. Controlled studies have confirmed that plasmapheresis shortens the interval to independent ambulation and the duration of mechanical ventilation. Plasmapheresis was recommended. Plasmapheresis and/or

immunosuppressive drugs are alternatives if IVIG is ineffective. Steroids are effective. Supportive care, such as respiratory support, prevention decubitus ulcers in children with flaccid tetraplegia, nutritional support, management, prevention of deep vein thrombosis, and treatment of secondary bacterial infections, is important.

An important part of the general support of the child with Guillain-Barré syndrome is physiotherapy. This should be started during convalescence, and both active and passive exercises should be graduated as recovery progress.

## PROGNOSIS

The clinical course is usually benign, and spontaneous recovery begins within 2–3 weeks. Most of the patients regain full muscular strength, although some are left with residual weakness. The tendon reflexes are usually the last function to recover. Improvement usually follows a gradient opposite the direction of involvement: bulbar function recovering first, and lower extremity weakness resolving last. Bulbar and respiratory muscle involvement can lead to death if the syndrome is not recognized and treated. Although prognosis is generally good and the majority of children recover completely, three clinical features are predictive of poor outcome with sequelae: cranial nerve involvement, intubation, and maximum disability at the time of presentation. The electrophysiologic features of conduction block are predictive of good outcome.

Long-term follow-up studies of patients who recover from an attack of Guillain-Barré syndrome reveal that many do have some permanent axonal loss, with or without residual clinical signs of chronic neuropathy. Easy fatigue is one of the most common chronic symptoms, but it is not the rapid fatigability of muscles seen in myasthenia gravis. Most patients with the axonal form of Guillain-Barré syndrome had a slow recovery over the first 6 months and could eventually walk, although some required years to recover. Electromyography and nerve conduction velocity electrophysiologic studies do not necessarily predict the long-term outcome.

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# Hydrocephalus

## PRESENTING COMPLAINTS

An 8-month-old boy was brought with the complaints of:

- Big head since 2 months
- Vomiting since 1 week

## History of Presenting Complaints

An 8-month-old boy was brought to the pediatric casualty with history of bouts of vomiting. It has started since 6–8 hours back. It was projectile in nature. Vomitus contained ingested food material, sometimes yellowish in color. The mother revealed similar attack of vomiting about 3 days back. For that child had taken treatment from the general practitioner. But, there was no loose motion. According to mother, her child was irritable. She had noticed that the head of the child was bigger than the other children of the same age group. There was no history of altered sensorium and convulsions.

### CASE AT A GLANCE

#### Basic Findings

Length	: 70 cm (85th centile)
Weight	: 8 kg (50th centile)
Head circumference	: 50 cm
Temperature	: 37°C
Pulse rate	: 116 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Vomiting
- Lower segment cesarean section (LSCS) delivery
- Delayed milestones

##### Examination

- Large head
- Sunset sign
- AF was large
- Prominent scalp veins

##### Investigation

- *CT scan*: Uniform dilatation of the ventricle
- *Hemoglobin*: Decreased

## Past History of the Patient

He was the first sibling of consanguineous marriage. He was born at term. He had been delivered by lower segment cesarean section (LSCS) for cephalopelvic disproportion. He cried immediately after the delivery. The birth weight was 2.5 kg. The head circumference was 36 cm. The length was 50 cm. He started taking breast milk. There was no significant postnatal event. He was on exclusively breastfeeds for 3–4 months. Weaning started later with cereals and fruits gradually. His developmental milestones are a bit delayed. He had been completely immunized.

## EXAMINATION

The child was moderately built and moderately nourished. These were signs of moderate dehydration. The head appeared larger with prominent forehead. White part of the sclera was visible above the pupil, i.e., sunset sign, the anterior fontanelle was large. There was splaying of sagittal suture. Transillumination test was positive.

The anthropometric measurements included, the length was 70 cm (85th centile), the weight was 8 kg (50th centile). The head circumference was 50 cm.

The child was afebrile, pulse rate was 116 per minute, and respiratory rate 20 per minute. Blood pressure was recorded 70/50 mm Hg. There was no pallor, no lymphadenopathy and no clubbing.

## INVESTIGATION

Hemoglobin	: 9 g/dL
TLC	: 9,600 cells/cu mm
ESR	: 26 mm in the 1st hour
CSF examination	: Normal
Plain X-ray skull	: Normal
CT scan	: Uniform dilatation of the ventricle

## DISCUSSION

The child was brought to the hospital with the history of projectile vomiting and not taking feeds

usually suggests some intracranial infection. This is again supported by large anterior fontanelle and sunset sign. Other findings such as large head, splaying of the sagittal suture, positive transillumination and cracked pot or Macewen's sign (hearing of cracked pot on percussion of the head) help in diagnosis of hydrocephalus.

Hydrocephalus is an excessive accumulation of cerebrospinal fluid (CSF) in the head. The hydrocephalus is usually caused by a disturbance of the CSF flow or its absorption.

## PHYSIOLOGY OF CEREBROSPINAL FLUID CIRCULATION

Hydrocephalus represents a diverse group of conditions that result from impaired circulation and/or absorption of CSF or, in rare circumstances, from increased production of CSF by a choroid plexus papilloma.

The CSF is formed primarily in the ventricular system by the choroid plexus, which is situated in the lateral, third, and fourth ventricles. Although most CSF is produced in the lateral ventricles, approximately 25% originates from extrachoroidal sources, including the capillary endothelium within the brain parenchyma. There is active neurogenic control of CSF formation because adrenergic and cholinergic nerves innervate the choroid plexus. Stimulation of the adrenergic system diminishes CSF production, whereas excitation of the cholinergic nerves may double the normal CSF production rate. In a normal child approximately 20 mL/h of CSF is produced. The total volume of CSF approximates 50 mL in an infant and 150 mL in an adult. Most of the CSF is extraventricular. The choroid plexus forms CSF in several stages through a series of intricate steps, a plasma ultrafiltrate is ultimately processed into a secretion—the CSF.

The CSF flow results from the pressure gradient that exists between the ventricular system and venous channels. Intraventricular pressure may be as high as 180 mmH<sub>2</sub>O in the normal state, whereas the pressure in the superior sagittal sinus is in the range of 90 mmH<sub>2</sub>O. Normally CSF flows from the lateral ventricles through the foramina of Monro into the 3rd ventricle. It then traverses the narrow aqueduct of Sylvius which is approximately 3 mm long and 2 mm in diameter in a child to enter the fourth ventricle. The CSF exits the fourth ventricle through the paired lateral foramina of Luschka and the midline foramen of Magendie into the cisterns at the base of the brain.

Hydrocephalus resulting from obstruction within the ventricular system is called obstructive

or noncommunicating hydrocephalus. The CSF then circulates from the basal cisterns posteriorly through the cistern system and over the convexities of the cerebral hemispheres. CSF is absorbed primarily by the arachnoid villi through tight junctions of their endothelium by the pressure forces that were noted earlier. CSF is absorbed to a much lesser extent by the lymphatic channels directed to the paranasal sinuses, along nerve root sleeves, and by the choroid plexus itself. Hydrocephalus resulting from obliteration of the subarachnoid cisterns or malfunction of the arachnoid villi is called nonobstructive or communicating hydrocephalus.

The primary function of CSF is to provide buoyancy and allow the brain to float, protecting it from repetitive trauma whenever the head moves. Movement of CSF through the foramen magnum compensates for the changes that occur in cerebral blood volume with each heartbeat. Slow circulation of CSF from the ventricular system of brain into the subarachnoid space is achieved by arterial pulsation in brain and choroid plexus and by changes in venous pressure responding to respiration, change in posture, exercise and coughing.

Cerebrospinal fluid absorption access the arachnoid granulations is passive and depends upon the pressure gradient between CSF and the superior sagittal sinus and the outflow resistance.

Cerebrospinal fluid is produced by active transport of Na<sup>+</sup> ions and passive transfer of water with Na<sup>+</sup> across the choroid plexus from the vascular compartment to the cerebral ventricle. From the lateral ventricle it moves via the foramen of Monro, third ventricle, aqueduct of Sylvius, fourth ventricle and foramen of Luschka and Magendie into the subarachnoid cistern. It is reabsorbed into the circulation through arachnoidal granulations (arachnoid villi) in the subarachnoid space.

The conventional model holds that CSF flows through the aqueduct, fourth ventricle and foramina of Luschka and Magendie to the cisterna magna. From there the CSF flows over the surface of the cerebral hemispheres to be reabsorbed into the bloodstream via the arachnoid granulations which contain the arachnoid villi.

## PATHOPHYSIOLOGY OF HYDROCEPHALUS

The major physiological abnormality in hydrocephalus is an imbalance of normal CSF formation and impaired absorption due to obstruction in flow of CSF. If CSF is retained within the cranial cavity the intracranial pressure must increase unless

compensatory mechanisms are available, with increased intracranial pressure, any additional fluid is forced into alternate pathways for absorption.

Obstruction to CSF flow leads to reversal of the transependymal movement of ventricular fluid into the periventricular white matter and is associated with a reduction in the local cerebral blood flow resulting in demyelination and progressive gliosis, if it is left untreated.

With acute hydrocephalus, the initial ventricular dilatation is accompanied by high intracranial pressure. Later intracranial pressure subsides to remain modestly raised (10–15 mm Hg), but ventriculomegaly progresses.

Choroid plexus papilloma is the only condition in which excess production has been adequately documented to produce hydrocephalus otherwise, any lesion that isolates the CSF producing structures from major sites of absorption will result in excessive accumulation of CSF within that part of the ventricular system. During 1st year of life, the most common causes are developmental abnormalities of brain.

Obstructive, also known as noncommunicating, hydrocephalus occurs when the CSF flow is blocked along the ventricles or along a passage connecting the ventricles, causing ventricular dilation proximal to the point of blockage. Obstruction may be congenital or acquired. Congenital hydrocephalus is estimated to occur at a rate of 1–2 per every 1000 live births, Aqueductal stenosis, due to stenosis of the Sylvian aqueduct connecting the third and fourth ventricles, is the most frequent cause of congenital hydrocephalus. Aqueductal stenosis results from an abnormally narrow aqueduct of Sylvius that is often associated with branching or forking. In a small percentage of cases, aqueductal stenosis is inherited as a sex-linked recessive trait. These patients occasionally have minor neural tube closure defects, including spina bifida occulta. Other etiologies include complications of myelomeningoceles and Chiari malformations that obstruct CSF outflow from the fourth ventricle. Acquired causes of obstructive hydrocephalus frequently are posterior fossa tumors, including medulloblastomas, astrocytomas, or ependymomas.

Intrauterine viral infection can also produce aqueductal stenosis followed by hydrocephalus, mumps meningoencephalitis has been reported as a cause in a child. A vein of Galen malformation can expand to become large and because of its midline position, obstruct the flow of CSF. Lesions or malformations of the posterior fossa

are prominent causes of hydrocephalus, including posterior fossa brain tumors, Chiari malformation, and the Dandy-Walker syndrome.

Nonobstructive, or communicating, hydrocephalus may be the result of excess CSF production or decreased absorption, which causes the dilation of the entire ventricular system. Increased production of CSF may occur in the case of a choroid plexus papilloma. Decreased absorption may result from central nervous system hemorrhage infection, inflammation, or increased venous pressure.

Nonobstructive or communicating hydrocephalus most commonly follows a subarachnoid hemorrhage, which is usually a result of intraventricular hemorrhage in a premature infant. Blood in the subarachnoid spaces can cause obliteration of the cisterns or arachnoid villi and obstruction of CSF flow. Pneumococcal and tuberculous meningitis have a propensity to produce a thick, tenacious exudate that obstructs the basal cisterns, and intrauterine infections can also destroy the CSF pathways. Leukemic infiltrates can seed the subarachnoid space and produce communicating hydrocephalus.

In preterm infants, intraventricular hemorrhages (IVHs) commonly lead to hydrocephalus. Preterm infants have IVH as a complication. Other sources of hemorrhage, including ruptured arteriovenous malformations, ruptured aneurysms, trauma, or bleeding disorders, may cause hydrocephalus by decreasing reabsorption at the arachnoid villi.

Congenital infections, such as TORCH (Toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes) infections, as well as acquired bacterial or viral meningitis, may lead to decreased absorption of CSF and hydrocephalus. Increased venous pressure, as seen in vein of Galen malformations, may lead to decreased resorption of CSF and hydrocephalus. Arnold-Chiari malformation is important cause of communicating hydrocephalus which occurs in association with spina bifida, meningocele and meningomyelocele.

#### ESSENTIAL DIAGNOSTIC POINTS

- Increased volume of CSF with progressive ventricular dilatation
- Hemorrhage, infection, tumors, and congenital malformation
- Macrocephaly, increased rate head growth
- Impaired extraocular movements
- Hypertonia of lower limbs, generalized hyper-reflexia
- Papilledema, optic atrophy infants

## CLINICAL FEATURES (FIG. 1)

Clinical presentation of hydrocephalus is variable and depends on many factors, including the age at onset, the nature of the lesion causing obstruction, and the duration and rate of increase of the intracranial pressure (ICP).

### Neonate/Infant

In an infant, an accelerated rate of enlargement of the head is the most prominent sign. In addition, the anterior fontanel is wide open and bulging, and the scalp veins are dilated. The forehead is broad, and the eyes might deviate downward because of impingement of the dilated suprapineal recess on the brainstem tectum, producing the setting—sun eye sign. Long-tract signs, including brisk tendon reflexes, spasticity, clonus (particularly in the lower extremities), and Babinski sign, are common owing to stretching and disruption of the corticospinal fibers originating from the leg region of the motor cortex.

Head circumference at birth is about 34 cm for term infant. The head circumference normally grows by 2 cm/month for the first 3 months of the life and 1 cm/month for 4–6 months and 0.5 cm/month up to 1 year of life.

Accurate serial recording of the head circumference is essential for early diagnosis of hydrocephalus and should be supported by serial USG. An increase in the head circumference in the first 3 months of life >1 cm every fortnight should arouse suspicion of hydrocephalus. Brain grows very rapidly in the first few weeks of life and therefore sagittal and coronal sutures may be separated up to 0.5 cm. This physiological

separation disappears after the first fortnight of life. Persistent widening of squamo-parietal sutures is not physiological and should arouse suspicion of hydrocephalus. Accurate serial recording of head circumference is required for early diagnosis of neonatal hydrocephalus. Widening of squamo-parietal suture is not physiological and should be considered as a suspicion of hydrocephalus.

In neonate, rapid head enlargement may be asymptomatic until irritability, poor appetite, vomiting and poor head control develop. Regular and accurate head circumference measurements are important in infants to detect hydrocephalus before clinical symptoms appear.

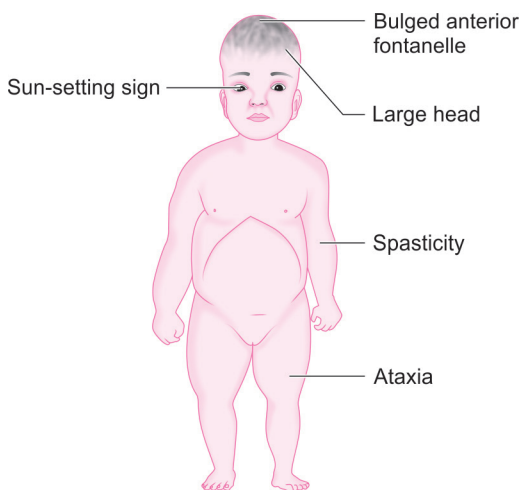
In hydrocephalus, the open fontanelle feel tense and fusion of the sutures is delayed, resulting in an enlarged head. The scalp veins become dilated because of raised intracranial pressure (**Fig. 2A**).

Late signs include:

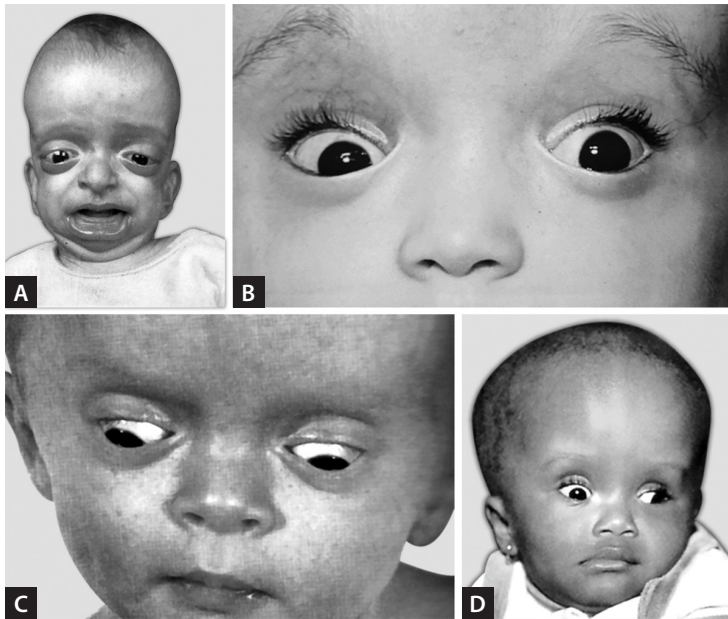
- The tympanitic sound obtained on percussing the vault of the thinned hydrocephalic skull Macewen's sign, i.e., resonant note on percussions of the skull is noted
- The scalp vein becomes dilated because of raised intracranial pressure
- Brilliant transillumination
- The 'setting sun' sign (paralysis of upward gaze and prominence of the upper part of the sclera resulting from pressure of the dilated third ventricle on the tectum of midbrain) (**Figs. 2B to D**).
- Papilledema is unusual in infants

### Older Children

In an older child, the cranial sutures are less accommodating so the signs of hydrocephalus may be subtler. Irritability, lethargy, poor appetite, and vomiting are common to both age groups, and headache is a prominent symptom in older patients. A gradual change in personality and deterioration in academic productivity suggest a slowly progressive form of hydrocephalus. With regard to other clinical signs, serial measurements of the head circumference often indicate an increased velocity of growth. Percussion of the skull might produce a cracked pot sound or Macewen sign, indicating separation of the sutures. A foreshortened occiput suggests Chiari malformation, and a prominent occiput suggests the Dandy-Walker malformation. Papilledema, abducens nerve palsies, and pyramidal tract signs, which are most evident in the lower extremities, are apparent in many cases.



**Fig. 1:** Clinical features.



**Figs. 2A to D:** (A) Enlarged head; (B to D) Sun-setting sign—hydrocephalus.

In older children, once the sutures begin to fuse, patients may present with raised intracranial pressure, headache often is worse early in the morning. Nausea, vomiting, blurred vision and later drowsiness leading depressed conscious state and death. Gait abnormalities are due to the stretching of paracentral corticospinal fibers of the parietal cortex by expanding lateral ventricle. The more nerve fibers that serve the lower extremities are compressed early producing wide based waddling gait.

## EXAMINATION

Examination includes careful inspection, palpation, and auscultation of the skull and spine. The occipitofrontal head circumference is recorded and compared with previous measurements. The size and configuration of the anterior fontanel are noted, and the back is inspected for abnormal midline skin lesions, including tufts of lipoma, or angioma that might suggest spinal dysraphism. The presence of a prominent forehead or abnormalities in the shape of the occiput can suggest the pathogenesis of the hydrocephalus. A cranial bruit is audible in association with many cases of vein of Galen arteriovenous malformation. Transillumination of the skull is positive with massive dilation of the ventricular system or in the Dandy-Walker syndrome. Inspection of the eyegrounds is mandatory because of the finding of chorioretinitis suggests an intrauterine infection,

such as toxoplasmosis, as a cause of the hydrocephalus. Papilledema is observed in older children but is rarely present in infants because the cranial sutures separate as a result of the increased pressure.

Child appears spastic or ataxic with gradual deterioration of the mental activity. Associated symptoms include headache, nausea and vomiting, irritability, apathy and drowsiness. Limbs become spastic because of stretching of cortical fibers. Distortion of the brainstem may lead to bradycardia, systemic hypertension and altered respiration.

### GENERAL FEATURES

- Resonant percussion of skull
- Dilated scalp veins
- Papilledema
- Spastic
- Ataxia

## DIAGNOSIS

Investigation of a child with hydrocephalus begins with the history. Familial cases suggest X-linked or autosomal hydrocephalus secondary to aqueductal stenosis. A past history of prematurity with intracranial hemorrhage, meningitis, or mumps encephalitis is important to ascertain. Multiple café au lait spots and other clinical features of neurofibromatosis point to aqueductal stenosis as the cause of hydrocephalus.



The head might appear enlarged (and can be confused with hydrocephalus) secondary to a thickened cranium resulting from chronic anemia, rickets, osteogenesis imperfecta, and epiphyseal dysplasia. Chronic subdural collections can produce bilateral parietal bone prominence. MRI has revealed the common occurrence of benign external hydrocephalus, a growth-limited condition where intervention is rarely required.

Various metabolic and degenerative disorders of the CNS produce megalencephaly as a result of abnormal storage of substances within the brain parenchyma. These disorders include lysosomal diseases (Tay-Sachs disease, gangliosidosis, and the mucopolysaccharidoses), the aminoacidurias (maple syrup urine disease and the leukodystrophies (metachromatic leukodystrophy, Alexander disease, Canavan disease)).

In addition, cerebral gigantism (Sotos syndrome), other overgrowth syndromes and neurofibromatosis arc characterized by increased brain mass. Familial megalencephaly is inherited as an autosomal dominant trait and is characterized by delayed motor milestones and hypotonia but normal or near-normal intelligence. Measurement of parents' head circumferences is necessary to establish the diagnosis.

## Cerebrospinal Fluid

Analysis of CSF both biochemistry and cellular components can provide additional information relative to the cause of hydrocephalus and may aid in directing therapy. In neonates and premature infants, elevation of red cell counts and xanthochromia, usually in association with low CSF glucose and elevated protein, suggest the diagnosis of intraventricular hemorrhage.

## Radiography

Plain X-rays in infants with hydrocephalus will reveal frontal bossing as well as macrocephaly. Separation of sutures is easily seen in older children but can be difficult in neonates. Enlargement of posterior fossa suggests possibility of Dandy-Walker's syndrome. In older children, a silver beaten appearance is early seen which is attributed to cortical impression against the inner table of the skull.

## Ultrasonography

Transfontanelle ultrasonography is useful in neonates because it is noninvasive and repeatable. Lateral ventricular size and morphology are easily

ascertained. Third ventricular size and shape is typically demonstrated, although delineation of the anatomy of the recess is variable. Ultrasound studies are less reliable for surface lesions, e.g., hydranencephaly, subdural or epidural collections and for subarachnoid hemorrhage. The visualization of fourth ventricle is usually difficult.

## Computed Tomography

Visualization of entire ventricular system by computed tomography (CT) provides valuable information about pathogenesis or cause. Moderate degrees of ventricular asymmetry are common in both normal and hydrocephalic brain. Dilatation of occipital and temporal horns tends to occur prior to marked enlargement of the frontal horns. Space occupying lesions of brain are easily seen after contrast administration.

If no areas of abnormal enhancement are visualized, the location of the ventricular obstruction will be indicated by the status of the fourth ventricle. If the fourth ventricle is normal or small, the obstruction is presumed to be proximal to this site, suggesting a diagnosis of aqueductal stenosis. Dilatation of the fourth ventricle suggests distal obstruction either at the outflow foramina of the fourth ventricle or within the subarachnoid pathways. Inoculation of contrast agent directly into the CSF by either lumbar puncture or by direct ventricular tap provides additional detail and may be of value in situations where exact location of obstruction is needed.

## Magnetic Resonance Imaging

The magnetic resonance (MR) studies provide more finer details if ventricular system not available by CT scans. Small obstructing lesions about the foramen of Monro or aqueduct of Sylvius and cyst of cisticercus larvae in fourth ventricle, often isodense on CT, are seen by magnetic resonance imaging (MRI). MRI is helpful in complex cases to define multiple congenital lesions and anatomy at the foramen magnum. Dynamic MRI can image the pattern of pulsatile CSF flow.

## Electroencephalography

The electroencephalography (EEG) is rarely of diagnostic value unless the hydrocephalus is accompanied by seizures. EEG is important in differentiating the absence of cerebral cortex (severe hydrocephalus). Significant therapeutic and prognostic differences exist between these two entities.

## Intracranial Pressure Monitoring

A saline-filled catheter or catheter-tipped transducer inserted into the lateral ventricle, brain or subdural space records a pulsatile pressure of 0–10 mm Hg relative to the foramen of Monro when patient is lying flat. As a mass or the ventricles enlarge within the skull, the mean intracranial pressure rises and spontaneous periodic waves become more pronounced particularly during rapid eye movement sleep.

### LABORATORY SALIENT FINDINGS

- X-ray of skull
- CT scan
- Ultrasonography
- MRI
- Electroencephalography
- Lumbar puncture: CSF analysis

## DIFFERENTIAL DIAGNOSIS

*Megalencephaly* refers to the increase in volume of brain parenchyma. There are no signs of increased intracranial pressure. The ventricles are neither large, nor under increased pressure. Causes include Hurler syndrome, metachromatic leukodystrophy and Tay-Sachs disease.

*Chronic subdural hematoma* causes large head, mostly located in the parietal region without prominent scalp veins or sunset sign. Large head size is also observed in hydranencephaly, rickets, achondroplasia, hemolytic anemia and familial macrocephaly.

The differential diagnoses of hydrocephalus include megalencephaly, chronic subdural hematoma, cerebral atrophy, and brain tumor.

## TREATMENT

Therapy for hydrocephalus depends on the cause. Medical management, including the use of acetazolamide and furosemide, can provide temporary relief by reducing the rate of CSF production, but long-term results have been disappointing. Most cases of hydrocephalus require extracranial shunts, particularly a ventriculoperitoneal shunt.

The cause of hydrocephalus should be treated and the obstruction of CSF outflow should be relieved as early as possible.

Carbonic anhydrase inhibitors (e.g., acetazolamide) decrease CSF production and in conjunction with corticosteroids or diuretics help to control hydrocephalus in premature infants until they are well enough to undergo surgery. In patients where hydrocephalus may be transient

(e.g., after subarachnoid hemorrhage), temporary CSF diversion may be carried out using a ventricular or lumbar catheter with careful control of the drainage pressure to avoid rerupture of any aneurysm.

In patients with noncommunicating hydrocephalus and where it is assumed that the subarachnoid space remains patent, a trans-ventricular, endoscopic third ventriculostomy may be performed, with puncture of the floor of the third ventricle and drainage of the CSF into the basal cisterns.

Endoscopic third ventriculostomy has evolved as a viable approach and criteria have been developed for its use, but the procedure might need to be repeated to be effective. Ventricular shunting may be avoided with this approach.

The major complications of shunting are occlusion (characterized by headache, papilledema, emesis, mental status changes) and bacterial infection (fever, headache, meningismus), usually caused by *Staphylococcus*. With meticulous preparation, the shunt infection rate can be reduced to <5%. The results of intrauterine surgical management of fetal hydrocephalus have been poor (possibly because of the high rate of associated cerebral malformations in addition to the hydrocephalus) except for some promise in cases of hydrocephalus associated with fetal meningomyelocele.

The CSF is usually drained from the ventricular cistern via a ventricular catheter (a valve with reservoir mechanism and a distal catheter) into the peritoneal cavity (historically almost every cavity and hollow organ in the body has been used).

Lumboperitoneal shunts are used to drain fluid from the lumbar subarachnoid space to the peritoneal cavity in some patients with communicating hydrocephalus and in those with benign intracranial hypertension. These shunts usually work well a few months only and where they are successful, may be associated with symptomatic secondary herniation of the cerebellar tonsils. It is helpful to insert a separate ventricular access device at the time of shunt procedure because it facilitates investigation if complications ensue.

Surgical intervention may not be required if hydrocephalus gets arrested spontaneously. Medical management include acetazolamide given in dose of 50 mg/kg/day. It diminishes CSF production in mild to moderate degree of hydrocephalus. Oral glycerol and isosorbide has also been used.

Surgical intervention is needed if size of the head enlarges rapidly or associated with progressive symptoms such as impairment of visions or life is affected before irreparable damage occurs.

In congenital obstructive hydrocephalus, a ventriculoarterial or ventriculoperitoneal shunt should be done. This will help to drain the CSF directly into circulation or into peritoneal cavity. As child grows in size it may be necessary to revise the shunt, using a longer tube.

Acute hydrocephalus may be managed by repeated lumbar puncture.

## COMPLICATIONS

The decision to insert a shunt is clear where there is active, progressive hydrocephalus, supported by radiological evidence of ventriculomegaly. However, the presence of ventriculomegaly in the absence of any supporting features does not mean there is active hydrocephalus and a shunt may be dangerous. Under, these circumstances, more detailed investigations, often repeated over months or years are necessary. The incidence of epilepsy attributable to shunt insertion is small. Trauma to the brain during shunt insertion is uncommon provided appropriate techniques are used.

*Underdrainage (malfunction):* The highest risk of underdrainage is in the 1st year (30%). It is usually caused by a gradual occlusion of the ventricular catheters by choroids plexus.

Plain radiographs can demonstrate disconnection. A CT brain scan is the best investigation for suspected underdrainage, especially if the scan can be compared with one infection. Contamination most often occurs at the time of insertion; 70% of infections appear within 1 month of insertion.

Many organisms may be responsible but the most common is *Staphylococcus epidermidis*. Aspiration of CSF from the shunt reservoir, under neurosurgical guidance, gives the best yield for the assessment of contamination, but its absence does not exclude shunt infection.

*Overdrainage:* The gravity effect caused by the hydrostatic column of CSF between the inlet and outlet of a shunt may cause some shunts to overdrain, particularly in tall patients. The siphon effect may produce slit-ventricle syndrome, subdural hematomas, encysted fourth ventricles or postshunt craniosynostosis. Antisiphon devices and flow—regulating valves have been developed to reduce the incidence of these complications.

*Slit ventricle syndrome:* In children with functioning CSF shunt symptoms of raised intracranial pressure

may develop which is characterized by small ventricles as determined by CT scan. It is believed that the ability of the ventricles to expand is impaired. The reduction in brain compliance has been attributed to subependymal gliosis.

Several causes have been suggested for slit ventricle syndrome, intermittent ventricular catheter, obstruction between the collapsed walls of the lateral ventricles, overdrainage of CSF and intracranial of hypertension with normal functioning shunt. Evaluation of the shunt is required before appropriate treatment is given.

## FOLLOW-UP

In a well child or adult, routine outpatient follow-up may be a waste of time because complications most commonly occur between visits. Careful instructions must be given to the family about the symptoms and signs that may suggest malfunction.

## PROGNOSIS

Prognosis depends on the underlying condition and type of hydrocephalus. In a group of newly diagnosed babies with treated nontumoral hydrocephalus, 70% would be expected to attend a normal school and have a normal intelligence quotient (IQ).

Prognosis depends on the cause of the dilated ventricles and not on the size of the cortical mantle at the time of operative intervention, except in cases in which the cortical mantle has been severely compressed and stretched. Hydrocephalic children are at increased risk for various developmental disabilities. The mean intelligence quotient is reduced compared with the general population, particularly for performance tasks as compared with verbal abilities. Many children have abnormalities in memory function. Vision problems are common, including strabismus, visuospatial abnormalities, visual field defects, and optic atrophy with decreased acuity secondary to increased ICP.

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## PRESENTING COMPLAINTS

A 3-year-old girl was brought with the complaints of:

- Fever since 4 days
- Not taking feeds since 2 days
- Vomiting since 1 day
- Abnormal movements since 5 minutes

## History of Presenting Complaints

A 3-year-old girl was brought by the mother with the history of convulsions since morning. Mother gave the history that her daughter developed tonic-clonic convulsions about 30 minutes back. It involved both the upper and lower limbs. The convulsions were continuous for 5 minutes. Later she was taken to nearby clinic. Convulsions was brought under control by intravenous administration of diazepam. After that the doctor referred the child to the hospital for further management.

### CASE AT A GLANCE

#### Basic Findings

Height	: 95 cm (75th centile)
Weight	: 13 kg (50th centile)
Temperature	: 39°C
Pulse rate	: 124 per minute
Respiratory rate	: 22 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Convulsions
- Fever
- Altered sensorium

##### Examination

- Altered sensorium
- Meningeal signs
- DTR exaggerated

##### Investigation

- ESR: Raised
- CSF: Turbid, polymorph cells present

Mother also gave history of fever since 4 days. Fever was moderate to high degree, intermittent which used to be relieved by antipyretics. Mother had also noticed that child was inactive and was not taking feeds properly since 3 days. There was history of vomiting since previous day. Child had vomited about 2–3 times. The vomiting was projectile in nature.

## Past History of the Patient

She was the only sibling of nonconsanguineous marriage. She was born at full term by normal delivery. Her birth weight was 3 kg. She started taking breast milk immediately after delivery. There was no significant postnatal event. Weaning was started in the 4th month and completed by 1 year. She was immunized completely and all the developmental milestones were normal.

## EXAMINATION

The girl was moderately built and nourished. She was in altered sensorium. She was not responding to oral commands. She was responding to the painful stimulus by resisting it. Anthropometric measurements included, the height was 95 cm (75th centile), the weight was 13 kg (50th centile). There were signs of moderate dehydration.

The child was febrile 39°C. The pulse rate was 124 per minute. The respiratory rate was 22 per minute regular. Blood pressure recorded was 70/50 mm Hg. There was no pallor, no lymphadenopathy, no cyanosis and no clubbing.

Higher mental functions could not be elicited as child was in altered sensorium status. She was not responding to oral commands. She was responding to the painful stimulus by resisting the stimulus. There was no motor and sensory involvement. No cranial nerve was involved. Hypertonia was present. Deep tendon reflexes were exaggerated. Neck rigidity was present and Kernig's sign was present. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 11.5 g/dL
TLC	: 12,000 cells/cu mm
DLC	: P <sub>68</sub> L <sub>28</sub> E <sub>2</sub> M <sub>2</sub>
ESR	: 30 mm in the 1st hour
X-ray chest	: Normal
Mantoux test	: Negative
CSF examination	: Turbid elevated cell count mainly polymorphs sugar was 20 mg/dL Gram stain : Normal

## DISCUSSION

Child came to the hospital with history of convulsions, fever and altered sensorium. The meningeal signs were present. As the history of the illness is of short duration, the diagnosis goes in favor of pyogenic bacterial meningitis.

Bacterial meningitis is one of the most potentially serious infections occurring in infants and older children. This infection is associated with a high rate of acute complications and risk of long-term morbidity. The incidence of bacterial meningitis is sufficiently high in febrile infants that it should be included in the differential diagnosis of those with altered mental status and other evidence of neurologic dysfunction.

## ETIOLOGY

The most common causes of bacterial meningitis in children older than 1 month of age are *Streptococcus pneumoniae* and *Neisseria meningitidis*. Bacterial meningitis caused by *S. pneumoniae* and *Haemophilus influenzae* type b has become much less common in developed countries since the introduction of universal immunization against these pathogens beginning at 2 months of age. Infection caused by *S. pneumoniae* or *H. influenzae* type b must be considered in incompletely vaccinated individuals or those in developing countries. Those with certain underlying immunologic (HIV infection, immunoglobulin [Ig] G subclass deficiency) or anatomic (splenic dysfunction, cochlear defects or implants) disorders also may be at increased risk of infection caused by these bacteria.

Bacterial meningitis remains a common disease. The important factors include age, status of host immune system, colonization of the nasopharynx with potential pathogens.

During the neonatal period, gram-negative bacilli (principally *Escherichia coli*), other enterobacteriaceae, Group B streptococci, *Pseudomonas* sp.,

*Listeria monocytogenes* are the major causative agents.

From 1 to 3 months of age the common causes are group B streptococci, the gram-negative organisms become less common while *Haemophilus influenzae*, *Neisseria meningitidis* begins to appear.

From 3 months to 3 years of age, *H. influenzae* is the most common cause of meningitis followed by *Streptococcus pneumoniae*.

The risk for the development of neonatal meningitis includes prematurity, septicemia and prolonged rupture of the membrane (PROM).

Alterations of host defense resulting from anatomic defects or immune deficits also increase the risk of meningitis from less-common pathogens such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, coagulase-negative staphylococci, *Salmonella* species, anaerobes, and *Listeria monocytogenes*. Patients with diminished host resistance are responsible for development of meningitis.

Bacteria enters the cerebrospinal fluid (CSF) by hematogenous route, direct extension or by direct implantation of bacteria. The pathological steps include nasopharyngeal colonization, cell invasion, blood stream invasion crossing the blood-brain barrier and entry in CSF and survival and replication of subarachnoid space.

## PATHOGENESIS AND PATHOPHYSIOLOGY

The organisms causing neonatal meningitis are usually acquired during passage down the birth canal, from the mother or the nursery environment. Colonization of the nasopharynx, umbilicus and gastrointestinal tract precedes invasion of the blood stream and meninges.

For the most common cause of meningitis, the bacteria must first attach to the epithelial cells in the nasopharynx. *H. influenzae* and *N. meningitidis* have pili, which attach to the specific receptors on host cells, the bacteria must evade the local secretory mucosal IgA antibody. All the major bacterial pathogens causing meningitis have IgA proteases that disarm IgA, thereby clearing the way to attachment.

The bacteria must pass through these cells and access the blood stream. Once in the blood stream, bacteria must survive the immune mechanism and arrive at central nervous system (CNS) capillaries. The most common organisms causing bacterial meningitis are able to avoid these host defenses in the blood stream by virtue of their anti-phagocytic and anticomplement nature of their polysaccharide capsule.



Most cases of bacterial meningitis are hematogenous in origin, thus bacterial agents reach, invade and replicate in the CSF. These pathological steps include:

- Nasopharyngeal colonization
- Nasopharyngeal epithelial cell invasion
- Blood stream invasion
- Bacteremia with intravascular survival
- Crossing of the blood-brain barrier and entry into the CSF
- Survival and replication in the subarachnoid space

Bacteria enters the CSF by any one of the, namely several possible routes:

- *Hematogenous*: Most common route through which bacteria enters the CSF. There occur seeding of the subarachnoid space from a distant focus of infection or spontaneous bacteremia from nasopharyngeal colonization with the pathogen.
- Direct extension of the invading bacteria into the subarachnoid space.
- Direct implantation of the bacteria into the subarachnoid space either due to trauma or surgical event.

From the CNS capillaries, the bacteria must penetrate the blood-brain barrier and cross into the subarachnoid space. The bacteria enter the CSF via capillaries in the choroids plexus of the lateral ventricles. Once in the CSF, bacteria can multiply freely because the CSF is virtually devoid of complement, antibody and phagocytic cells. Even with the emergence of inflammation and the ingress of cells, complement and antibody into the CSF, the infection generally continues to progress.

Interstitial brain edema is the main pathological change. Brain edema is further induced by presence of arachidonic acid and its metabolites. These are released from the damaged cells of CNS and by the fatty acids released from polymorphonuclear leukocytes. The specific adhesion molecule causes adhesion to those epithelial cells and further provokes disruption of blood-brain barrier. All these factors lead to the increase in brain edema and decrease in the perfusion of the brain due to increased intracranial pressure and endothelial cell vasculitis and thrombosis. The final outcome of these processes is ischemic damage to the CNS.

The leptomeninges are infiltrated with inflammatory cells. The cortex of the brain shows edema, exudate and proliferation of microglia. Ependymal cells are destroyed purulent exudate collects at the base of the brain. Exudate may

block foramina of Luschka and Magendie and produces hydrocephalus. Permanent neurological sequela results from infarction, necrosis and hydrocephalus. Deaths may occur as result of endotoxic shock.

A meningeal purulent exudate of varying thickness may be distributed around the cerebral veins, venous sinuses, convexity of the brain, and cerebellum, and in the sulci, sylvian fissures, basal cisterns, and spinal cord. Ventriculitis with bacteria and inflammatory cells in ventricular fluid may be present (more often in neonates), as subdural effusions and, rarely, empyema. Perivascular inflammatory infiltrates may also be present, and the ependymal membrane may be disrupted.

Vascular and parenchymal cerebral changes characterized by polymorphonuclear infiltrates extending to the subintimal region of the small arteries and veins, vasculitis, thrombosis of small cortical veins, occlusion of major venous sinuses, necrotizing arteritis producing subarachnoid hemorrhage. Cerebral infarction, resulting from vascular occlusion because of inflammation, vasospasm, and thrombosis, is a frequent sequelae.

Inflammation of spinal nerves and roots produces meningeal signs, and inflammation of the cranial nerves produces cranial neuropathies of optic, oculomotor, facial, and auditory nerves. Increased intracranial pressure (ICP) also produces oculomotor nerve palsy because of the presence of temporal lobe compression of the nerve during tentorial herniation. Abducens nerve palsy may be a nonlocalizing sign of elevated ICP.

Increased ICP is a result of cell death (cytotoxic cerebral edema), cytokine-induced increased capillary vascular permeability (vasogenic cerebral edema), and, possibly, increased hydrostatic pressure (interstitial cerebral edema) after obstructed reabsorption of CSF in the arachnoid villus or obstruction of the flow of fluid from the ventricles. ICP may exceed 300 mmH<sub>2</sub>O; cerebral perfusion may be further compromised if the cerebral perfusion pressure (mean arterial pressure minus ICP) is <50 cmH<sub>2</sub>O as a result of systemic hypotension with reduced cerebral blood flow. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion may produce excessive water retention and potentially increase the risk of elevated ICP.

Hydrocephalus can occur as an acute complication of bacterial meningitis. It most often takes the form of a communicating hydrocephalus caused by adhesive thickening of the arachnoid villi around the cisterns at the base of the brain. Thus,

there is interference with the normal resorption of CSF. Less often, obstructive hydrocephalus develops after fibrosis and gliosis of the aqueduct of Sylvius or the foramina of Magendie and Luschka.

Raised CSF protein levels are partly a result of increased vascular permeability of the blood-brain barrier and the loss of albumin-rich fluid from the capillaries and veins traversing the subdural space. Continued transudation may result in subdural effusion, usually found in the later phase of acute bacterial meningitis.

Recurrent meningitis may be associated with pilonidal sinus, cerebrospinal fluid rhinorrhea, traumatic lesion of cribriform plate, ethmoidal sinus or congenital fistula.

### CLINICAL FEATURES (FIG. 1)

The clinical signs and symptoms of meningitis vary greatly depending on the age of the child and duration of the illness. The disease may have acute or insidious presentation.

Acute presentation is with headache, fever, altered mental status. While in insidious presentation the illness develops over several days to a week and pneumonia. Sinusitis, otitis media are present more commonly.

The onset of acute meningitis has two predominant patterns. The more dramatic and, fortunately, less common presentation is sudden onset with rapidly progressive manifestations of shock, purpura, disseminated intravascular coagulation, and reduced levels of consciousness often resulting in progression to coma or death within 24 hours. More often, meningitis is preceded by several days of fever accompanied by upper respiratory tract

or gastrointestinal symptoms, followed by non-specific signs of CNS infection, such as increasing lethargy and irritability.

Alterations of mental status are common among patients with meningitis and may be the consequence of increased ICP, cerebritis hypotension; manifestations include irritability, lethargy, stupor obtundation, and coma. Comatose patients have a poor prognosis.

The common and classic triad of fever, headache, stiff neck is quite variable depending upon the age group and virulence of the organisms. The factors other than age that determine the clinical manifestations include the degree of meningeal infection and inflammation, the presence of increased ICP (headache, vomiting, bulging fontanelle, papilledema): the occurrence of vasculitis or venous thrombosis (hemiparesis, other focal neurological deficits, seizures) and the development of subdural effusion (hemiparesis, seizures).

In the later onset disease fever, seizures, irritability, meningismus, bulging fontanelle are more likely to be observed. Bacterial meningitis in older children and young adults usually presents with the classic signs and symptoms of fever, headache, photophobia, nausea, vomiting and meningismus. Fever is almost always present.

Meningeal irritation may be suggested by the presence of a positive Brudzinski sign and Kernig sign. These signs of meningeal irritation are seen in up to 50% of older children and 90% of adults. Lethargy and confusion are more common in bacterial than with viral meningitis and the altered mental status is a consistent finding in older children. Headache is usually intense and severe. With pneumococcal meningitis, and associated pulmonary, ear or sinus infection is often found.

Focal neurological deficit (cranial neuropathies, seizures, hemiparesis) may relate to cerebritis or CNS infarction secondary to large vessel vasculitis or dural sinus thrombosis. Focal deficit should prompt investigation for brain abscess, subdural effusion or empyema.

Convulsions occur in 20–30% of children with meningitis. The seizures are usually generalized and do not necessarily indicate a poor prognosis. Focal seizure and focal neurological signs indicate the possible presence of cortical venous or arterial thrombosis with cortical infarct and suggest a less favorable prognosis. Seizures that occur on presentation or within the first 4 days of onset are usually of no prognostic significance. Seizures that persist after the 4th day of illness and those that

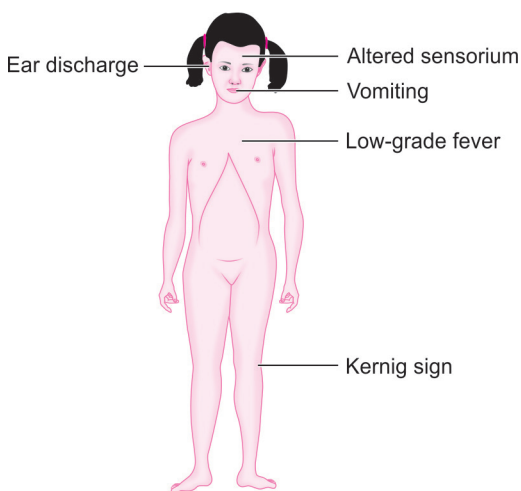


Fig. 1: Clinical features.

are difficult to treat may be associated with a poor prognosis.

Febrile seizures are common with streptococcal meningitis and *H. influenzae* meningitis. Convulsions occurring during an upper respiratory tract infection are common and must be distinguished from convulsions occurring with meningitis.

In older children lumbar puncture (LP) is unnecessary after a febrile convulsion, if meningitis is not suspected clinically. However, in children under 18 months of age in whom the signs of meningitis are subtle, CSF examination may be necessary to exclude meningitis. Ataxia may be the presenting feature with *H. influenzae* meningitis.

Cutaneous manifestations are an important early clue to some form of meningitis. A rapidly spreading purpuric rash (Fig. 2) is characteristic of meningococcal septicemia, but is also occasionally seen with pneumococcal or *H. influenzae* sepsis.

Papilledema due to raised ICP is an uncommon finding in acute bacterial meningitis but if present indicates subdural effusion, empyema or brain abscess. Cranial nerves VI, VII, IV and VIII are most commonly affected during acute bacterial meningitis.

Symptoms and signs found in newborn are vacant stare, irritability and drowsiness, persistent vomiting with fever, poor tone, poor cry, shock and circulatory collapse, refusal to feed, fever or hypothermia, convulsions and tremors. Petechial hemorrhages on the skin and mucous membrane are seen in meningococcal meningitis.

The diagnosis is more difficult in the neonatal period and in young infants when the signs are subtle and nonspecific. Fever is present in only half of neonates with meningitis. Lethargy, disinterest in feeding, vomiting or diarrhea, jaundice, respiratory

distress are common presenting features. Irritability and abnormal muscle tone are present in one-third of neonates with meningitis. Convulsion and a bulging fontanelle are late manifestations. As no sign is specific for meningitis, a high index of suspicion is necessary in assessing any ill-neonate or infant.

Sepsis hypotension, hypoxemia and increased intracranial pressure all contribute to the reduction of the perfusion of CNS. Fluid restriction has been recommended as a management of SIADH. A reasonable approach is to give two-thirds of daily fluid maintenance volume.

#### ESSENTIAL DIAGNOSTIC POINTS

- Fever
- Headache with projectile vomiting
- Altered sensorium, irritability
- Convulsions
- Meningeal irritation signs
- CSF findings
- CT scan
- MRI
- Focus of infection

#### GENERAL FEATURES

- Loss of appetite
- Papilledema
- Motor deficits

### DIAGNOSIS

As early diagnosis of meningitis is extremely important, it should be suspected in any child with lethargy, unconsciousness, inability to feed, stiff neck and seizures. It is important to note that the absence of fever or meningeal signs does not exclude the diagnosis of bacterial meningitis.

Blood cultures should be performed in all patients with suspected meningitis. Blood culture reveal the responsible bacteria in up to 80–90% of cases of meningitis. Elevations of the C-reactive protein, erythrocyte sedimentation rate, and procalcitonin have been used to differentiate bacterial (usually elevated) from viral causes of meningitis.

#### CSF Examination

The diagnosis of acute pyogenic meningitis is confirmed by analysis of the CSF, which typically reveals microorganisms on Gram stain and culture, a neutrophilic pleocytosis, elevated protein, and reduced glucose concentrations. LP should be performed when bacterial meningitis is suspected.

Acute bacterial meningitis should be suspected in children presenting with a brief history of fever,



**Fig. 2:** Purpuric rash of meningococcus.  
(For color version see Plate 2)

TABLE 1: CSF characteristics in acute bacterial meningitis.

Characteristics	Bacterial meningitis
CSF cells counts (cells/cu mm)	Polymorphonuclear >5–10000
CSF glucose	<10–50 mg/dL
CSF/Serum glucose ratio	0.3–0.5
CSF protein	100–500 mg/dL
CSF Gram stain/culture	90% positive

irritability, photophobia, headache, vomiting, convulsions and altered sensorium. Diagnosis should be substantiated by examination of the cerebrospinal fluid.

Contraindications for an immediate LP include (1) evidence of increased ICP (other than a bulging fontanel), such as 3rd or 6th cranial nerve palsy with a depressed level of consciousness, or hypertension and bradycardia with a respiratory abnormalities, (2) severe cardiopulmonary compromise requiring prompt resuscitative measures for shock or in patients in whom positioning for the LP would further compromise cardiopulmonary function, and (3) infection of the skin overlying the site of the LP.

Gram stain and culture of the CSF will result in identification of the bacteria in most cases of bacterial meningitis. CSF and blood culture should be taken before initiating antibiotics. The **Table 1** shows the typical CSF finding in bacterial meningitis. The CSF is usually cloudy and contains several hundreds to thousands of white blood cell (WBC), predominant polymorphonuclear leukocytes. CSF leukocytosis of greater than 10,000 cells/cu mm should suggest the presence of brain abscess or parameningeal abscess with rupture into subarachnoid space.

Cerebrospinal fluid glucose concentration is usually low in bacterial meningitis (i.e., less than 50% of simultaneous serum concentration) with levels ranging from less than 10 to 50 mg/dL. The ratio of CSF/serum glucose in bacterial meningitis should be less than 0.3 but no higher than 0.5. CSF protein concentrations are elevated (usually greater than 100 mg/dL). If there is marked protein concentration, a subarachnoid block of CSF flow should be suspected.

Rapid Diagnostic Tests

The development of rapid tests of CSF for the detection of specific bacterial antigens or the presence

of endotoxin from gram-negative bacteriae has helped in establishing the diagnosis of bacterial meningitis.

Rapid diagnostic tests may be used to distinguish between viral, bacterial and tuberculous meningitis based on antigen or antibody demonstration, e.g., countercurrent immunoelectrophoresis, latex particle agglutination, conglutinations, enzyme-linked immunosorbent assay (ELISA), and other techniques. Besides being rapid, they are unaltered by previous antibiotic usage. Latex agglutination and ELISA have sensitivity and specificity of almost 80%. Polymerase chain reaction (PCR) is used for diagnosis of infection with herpes simplex, enteroviruses, meningococci and tuberculosis.

The available diagnostic tests include latex particle agglutination (LPA) kits that contain antisera directed against the specific capsular antigens of *H. influenzae*, *S. pneumoniae*, *N. meningitidis*, coagulation tests (COA) and counter immune electrophoresis (CIE) tests are also of use. These tests have sensitivity and specificity between 50 and 90%.

INDICATIONS FOR CT SCAN

- Prolonged irritability
- Prolonged obtundation
- Seizures—3rd day of therapy
- Focal seizures
- Focal neurologic deficits
- Increasing head circumference
- Recurrence of disease

Computed tomography/MRI is useful in patients with raised intracranial pressure or with focal neurological signs and in these may reveal the presence of brain abscess, subdural effusion, hydrocephalus, infarction secondary to vasculitis or dural sinus thrombosis. Inflammation of the meninges can be demonstrated with contrast CT scan or MRI. The role of CT or MRI in meningitis is to exclude other CNS lesions or sequelae of bacterial meningitis.

LABORATORY SALIENT FINDINGS

- Lumbar puncture: CSF analysis
- Serological, immunological nucleic detection (PCR) test
- CT scan
- MRI
- Brain biopsy

Organism Identification

*CSF Gram stain:* It is quick, reliable and inexpensive, positivity depends on the number of



organisms in the CSF—at least  $10^5$  colony forming units/mL of CSF is required. The yield is markedly increased by examining fresh centrifuged sediment of the CSF.

**Acridine orange:** It stains the nucleic acid of some bacteria so that they appear bright red orange under a fluorescent microscope. It stains the intracellular bacteria better than the Gram stain and may be positive even when the Gram stain is negative.

**CSF culture:** A positive CSF culture is the gold standard for organism identification. High positivity (75%) reported from developed countries is not seen in developing countries because of prehospital antibiotic therapy, delayed plating, inadequate storage and transport of CSF.

**Samples from other site of infection:** Samples from other sites of infection such as pleural fluid, cellulitis, aspiration of petechiae in suspected meningococemia, and urine in young infants should also be collected for organism identification.

## DIFFERENTIAL DIAGNOSIS

**Meningism:** This may occur in inflammatory cervical lesions, apical pneumonia and in toxemia due to typhoid, influenza. There are no neurological signs and the cerebrospinal fluid is normal.

**Partially treated bacterial meningitis:** If the child has received prior antibiotics, the cerebrospinal fluid becomes sterile. Biochemistry may be altered and pleocytosis persists, though type of cellular response changes. It poses a difficult problem in the differential diagnosis from tuberculous meningitis and aseptic meningitis. The onset, clinical course; rapid diagnostic tests and other ancillary investigations may be useful.

**Aseptic meningitis:** The clinical and laboratory profile is similar to pyogenic meningitis. The CSF pressure is elevated, shows mild pleocytosis and moderate increase in protein with near normal sugar. The CSF lactic acid is not elevated. No organisms are cultured.

**Tuberculous meningitis:** The onset is insidious with lethargy, low-grade fever, irritability, vomiting, and weight loss. Features of meningeal irritation are less prominent and course of the illness is prolonged. Neurological features include seizures, gradually progressive unconsciousness, cranial nerve deficits, motor deficits, and visual involvement. Features of hydrocephalus and decerebration are relatively common. Evidence of systemic tuberculosis and family contact should be looked for.

Mantoux test may be positive and there may be evidence of tuberculosis elsewhere. CSF shows 100–500 cells, with majority of lymphocytes; sugar is less reduced than in pyogenic meningitis and protein is elevated.

**Cryptococcal meningitis:** It usually occurs in an immunocompromised host. There is low-grade fever, mild cough, and pulmonary infiltration. Meningeal involvement has a gradual onset with a protracted course. The clinical features are not specific. The CSF shows the fungus as thick walled budding yeast cells, surrounded by a large gelatinous capsule in India ink preparation. The organism grows well on Sabouraud medium.

**Viral encephalitis:** Acute onset with early disturbances of sensorium, raised intracranial pressure and variable neurological deficit. The CSF is clear, may show mild pleocytosis; mild elevation of protein and normal sugar. PCR for viral antigens and rising CSF antibody titers are useful diagnostic clues.

**Subarachnoid hemorrhage:** Sudden headache and sensorial alteration occur without preceding fever. The course of illness is rapid and signs of meningeal irritation are marked. CT scan is diagnostic. CSF reveals crenated red blood cells (RBCs).

**Lyme disease:** It is an infection of CNS with *Borrelia burgdorferi*, a tick-borne spirochete. Patients develop encephalopathy, polyneuropathy, leuko-encephalitis and hearing loss.

## COMPLICATIONS

Complication of acute bacterial meningitis can develop early in the course of disease or it may be a long-term late sequelae. Apart from early and late meningeal complications, systemic complications can develop during the illnesses and are associated with high mortality and requires specific therapeutic intervention.

Main neurological complications developing during the course of illness are ventriculitis, subdural effusion, neurological deficits, e.g., hemiparesis, quadriparesis, cranial nerve palsy, hydrocephalus, hearing loss, arachnoiditis, and mental retardation.

Late complications and sequelae are mental retardation, seizures, sensory neural hearing loss, visual impairment, behavioral problems, motor deficit, ataxia, and hydrocephalus.

## TREATMENT

Treatment of acute pyogenic meningitis falls into two categories. Antibacterial chemotherapy and



**TABLE 2:** Recommended antibiotics for initial treatment of meningitis in different age groups.

Age group	Drug	Dose (mg/kg/day)	
		0–7 days	7–28 days
Neonates	Ampicillin and Gentamicin	100–150	150–200
	or	5	7.5
	Ampicillin and Cefotaxime	100–150	150–200
	or Ceftazidime	100	150–200
Infants and children	Ampicillin and Chloramphenicol	200–300	
	or	75–100	
	3rd generation cephalosporins:		
	• Cefotaxime	200	
	• Ceftriaxone	100	
	• Ceftazidime	150	

specific measures designed to reverse systemic and neurological complications. The ideal antibiotic (**Table 2**) for a bacterial pathogen causing meningitis is the one that:

- Penetrates the blood-brain barrier and achieve CSF concentration at least 10 times greater than the minimal bactericidal concentration for the organisms
- Is nontoxic to the patient
- Is bactericidal and not bacteriolytic
- Does not promote emergence of resistance and sterilizes the CSF quickly

**Initial Antibiotic Therapy**

The initial (empirical) choice of therapy for meningitis in immunocompetent infants and children is primarily influenced by the antibiotic susceptibilities of *S. pneumoniae*. In contrast, most strains of *N. meningitidis* are sensitive to penicillin and cephalosporins, although rare resistant isolates have been reported. Approximately 30–40% of isolates of *H. influenzae* type b produce  $\beta$ -lactamases and, therefore, are resistant to ampicillin. These beta-lactamase-producing strains are sensitive to the extended-spectrum cephalosporins.

Based on the substantial rate of resistance of *S. pneumoniae* to  $\beta$ -lactam drugs, vancomycin (60 mg/kg/24 h, given every 6 hours) is recommended as a part of initial empirical therapy.

Because of the efficacy of third-generation cephalosporins in the therapy of meningitis caused by sensitive *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type b, cefotaxime (300 mg/kg/24 h, given every 6 hours) or ceftriaxone (100 mg/kg/24 h administered once per day or 50 mg/kg/dose, given every 12 hours) should also be used in initial empirical therapy. Patients allergic to beta-lactam antibiotics and >1 month of age can be treated with chloramphenicol (100 mg/kg/24 h, given every 6 hours).

If *L. monocytogenes* infection is suspected, as in young infants or those with a T-lymphocyte deficiency, ampicillin (200 mg/kg/24 h, given every 6 hours) should also be given because cephalosporins are inactive against *L. monocytogenes*. Intravenous trimethoprim sulfamethoxazole is an alternative treatment for *L. monocytogenes*.

If a patient is immunocompromised and gram-negative bacterial meningitis is suspected, initial therapy might include ceftazidime and an aminoglycoside or meropenem.

In neonatal bacterial meningitis, the list of likely pathogens is covered by regimen of ampicillin and gentamycin. The use of third generation cephalosporins alone (cefotaxime, ceftriaxone, ceftazidime) does not adequately treat the *Enterococcus* or *Listeria*. Therefore, the combination of ampicillin and gentamycin is appropriate until the infecting pathogen has been defined by culture. Since the blood-brain barrier has not fully formed at this age, aminoglycosides enter the CSF in adequate concentration via the intravenous route.

Intraventricular administration of gentamycin is indicated if the meningitic process is unresponsive and that too when the gram-negative bacteria are unresponsive to newer cephalosporins. The routine and direct instillation of aminoglycosides intraventrically should be avoided in neonatal meningitis because of the worse morbidity and mortality associated with this route of administration.

Seizures are common during the course of bacterial meningitis. Immediate therapy for seizures includes intravenous diazepam (0.1–0.2 mg/kg/dose) or lorazepam (0.05–0.10 mg/kg/dose), and careful attention paid to the risk of respiratory suppression. Serum glucose, calcium, and sodium levels should be monitored. After immediate management of seizures, patients should receive phenytoin (15–20 mg/kg loading dose, 5 mg/kg/24 h maintenance) to reduce the likelihood of recurrence. Phenytoin is preferred to phenobarbital because it produces less CNS depression

and permits assessment of a patient's level of consciousness. Serum phenytoin levels should be monitored to maintain them in the therapeutic range (10–20 µg/mL). The subsequent oral dose of 5 mg/kg/day for 3–4 weeks. If the child is unconscious feeding is done through nasogastric tube.

In older children and adults, use of the newer third generation cephalosporins is recommended in the initial empiric regimen and when the pathogen has been defined and its antibiotic sensitivity known, therapy may be simplified. Penicillin G is the drug of choice for the *Pneumococcus* and *Meningococcus*. *H. influenzae*, *S. pneumoniae* and *N. meningitidis* are sensitive to cephalosporins.

In the patients with severely immunocompromised host the additional pathogen to cover is *Listeria*. In *Listeria*, trimethoprim/sulfamethoxazole may be the antibiotic of choice.

The duration of antibiotic treatment for neonatal meningitis has been 2–3 weeks. If intraventricular antibiotics are used, a daily dose of 3–5 days is usually sufficient to sterilize the CSF compartment. The duration of antimicrobial therapy given via the intravenous route for the treatment of most cases of bacterial meningitis is 7–10 days. Longer duration of therapy (2–3 weeks) is recommended for staphylococcal and gram-negative bacillary meningitis.

Therapy for uncomplicated penicillin-sensitive *S. pneumoniae* meningitis should be for 10–14 days with a third-generation cephalosporin or intravenous penicillin (400,000 units/kg/24 h, given every 4–6 hours). If the isolate is resistant to penicillin and the third-generation cephalosporin, therapy should be completed with vancomycin. Intravenous penicillin (300,000 units/kg/24 h) for 5–7 days is the treatment of choice for uncomplicated *N. meningitidis* meningitis.

Uncomplicated *H. influenzae* type b meningitis should be treated for 7–10 days. Patients who receive intravenous or oral antibiotics before LP and who do not have an identifiable pathogen, but do have evidence of an acute bacterial infection on the basis of their CSF profile, should continue to receive therapy with ceftriaxone or cefotaxime for 7–10 days. If focal signs are present or the child does not respond to treatment, a parameningeal focus may be present and a CT or MRI scan should be performed.

Meningitis caused by *Escherichia coli* or *P. aeruginosa* requires therapy with a third-generation cephalosporin active against the

isolate in vitro. Most isolates of *E. coli* are sensitive to cefotaxime or ceftriaxone and most isolates of *P. aeruginosa* are sensitive to ceftazidime. Gram-negative bacillary meningitis should be treated for 3 weeks or for at least 2 weeks after CSF sterilization, which may occur after 2–10 days of treatment.

#### MINIMUM DURATION OF THERAPY

- *Meningococcal meningitis*: 5 days
- *H. influenzae meningitis*: 7–10 days
- *Pneumococcal meningitis*: 10 days
- *Group B streptococcal meningitis*: 14–21 days
- *Listeria monocytogenes meningitis*: 14–21 days
- *Gram-negative bacilli meningitis*: 21 days

### Supportive Therapy

Sepsis, hypotension, hypoxemia and increased intracranial pressure all contribute to a reduction in perfusion of the CNS.

Supportive measures to maintain an adequate circulation to the CNS should include reversal of hypoxemia and hypercarbia, intubation and ventilatory support may be necessary for this purpose. Increased PaCO<sub>2</sub> cause cerebral vasodilatation and thereby worsen intracranial pressure. Hyperventilation may be beneficial by causing vasoconstriction and thus reducing cerebral blood volume and decreasing intracranial pressure.

Fluid restriction during the first several days in bacterial meningitis has been recommended as a management of the SIADH. A reasonable approach is to give approximately two-thirds of the daily fluid maintenance volume.

Mannitol (0.5 g/kg given intravenously over 20 minutes) can be used to decrease cerebral edema by osmotic movement of fluid from edematous brain tissue to the intravascular compartment. Mannitol can be given repeatedly over a 24-hour period to a total maximum dose of 2 g/kg. Dexamethasone may reduce vasogenic brain edema by a direct effect on vascular endothelial cells.

Subdural effusion develops in 15–30% of patients with bacterial meningitis who are less than 2-year-old. These effusions are usually benign and need not be surgically drained unless they are causing a clinically significant increase in intracranial pressure. Subdural empyema is treated by drainage of the subdural space. Hydrocephalus is treated by shunt.

Subdural empyema is treated by drainage of the subdural space. Hydrocephalus is treated by shunt.

## Corticosteroids

Rapid killing of bacteria in the CSF effectively sterilizes the meningeal infection, but releases toxic cell products after cell lysis (cell wall endotoxin) that precipitate the cytokine-mediated inflammatory cascade. The resultant edema formation and neutrophilic infiltration may produce additional neurologic injury with worsening of CNS signs and symptoms. Therefore, agents that limit production of inflammatory mediators may be of benefit to patients with bacterial meningitis.

Corticosteroids appear to have maximum benefit if given 1–2 hours before antibiotics are initiated. They also may be effective if given concurrently with or soon after the first dose of antibiotics. Complications of corticosteroids include gastrointestinal bleeding, hypertension, hyperglycemia, leukocytosis, and rebound fever after the last dose.

Glucocorticoids have been shown to decrease the inflammatory response in the subarachnoid space and has marked influence on cytokine generation. Data support the use of intravenous dexamethasone, 0.15 mg/kg/dose given every 6 hourly for 5 days, in the treatment of children older than 6 weeks with acute bacterial meningitis—caused by *H. influenzae* type b. It is useful in preventing hearing loss and short-term neurological sequel. Among children with meningitis caused by *H. influenzae* type b, corticosteroid recipients have a shorter duration of fever, lower CSF protein and lactate levels, and a reduction in sensorineural hearing loss. Adjunctive dexamethasone therapy is potentially beneficial in children particular those with *H. influenzae* disease. The mechanism of the beneficial effect of steroid is not completely clear.

## Specific Antibiotic Therapy

Meningococci	: Penicillin 4–5 lac units/kg/day 4 hourly Cefotaxime 200 mg/kg/day 8 hourly Ceftriaxone 150 mg/kg/day 12 hourly
<i>H. influenzae</i>	: Ceftriaxone, cefotaxime Ampicillin 300 mg/kg/day IV 6 hourly
<i>Pneumococcus</i>	: Cefotaxime or ceftriaxone
Staphylococci	: Vancomycin is used

## PROGNOSIS

The morbidity and mortality is associated with bacterial meningitis are clearly related to host (age, immune status), the organism (virulence factors) and the adequacy of therapy. Untreated bacterial meningitis is usually fatal.

Mortality rates in neonates with gram-negative bacillary meningitis is 50%. Mortality rates for *H. influenzae* is 3–5% and *N. meningitidis*, *S. pneumoniae*. The mortality with group B streptococci meningitis is related with the age of onset, pneumococcal meningitis carries the greatest risk of hearing impairment and highest mortality than with any other organism.

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# Meningomyelocele

## PRESENTING COMPLAINTS

A newborn male baby was brought with the complaint of swelling in the lower back since birth.

## History of Presenting Complaints

A 1-day-old male baby was brought to the neurosurgery department with history of swelling at the lower back. The resident doctor who attended the delivery noticed the small swelling in the midline at the lower back. He thought it as the defect in the vertebral arch or the neural tube and hence referred to neurosurgical department. The child passed urine and meconium. The movements in all the limbs were normal.

## Past History of the Patient

He was the first child of nonconsanguineous marriage. He was born at full term and delivered by cesarean section. The indication for the section was breech presentation. The child cried immediately after the delivery. Small swelling was noticed at the back. The child had all the neonatal reflexes satisfactory. He started taking breast milk. He had transient tachypnea which settled by itself within 24 hours.

## EXAMINATION

The boy was moderately built and nourished. He was active and sleeping. All the neonatal reflexes were satisfactory. He had good swallowing, sucking and rooting reflexes. He had passed urine without dribbling. He had passed meconium.

Anthropometric measurements included, the length was 49 cm (25th centile), the weight was 3 kg (25th centile) and the head circumference was 36 cm. There was no pallor, no edema. He was afebrile. The heart rate was 136 per minute, the respiratory rate was 28 per minute, and blood pressure recorded was 50/30 mm Hg.

There was a midline defect in skin of the back. The defect was covered by transparent membrane. It appeared as a small swelling. Under the transparent membrane, neural tissue was attached to inner surface. Other systemic examination was normal.

## INVESTIGATIONS

Hemoglobin	: 14 g/dL
TLC	: 9,800 cells/cu mm
CT scan of head	: Normal
MRI of the spine	: Normal

## DISCUSSION

Meningomyelocele is the midline defect of the skin, vertebral arch and neural tube (**Figs. 1A to C**). It is usually in the lumbosacral region. It is evident at birth as a skin defect over the back bordered laterally by bony prominences of unfused neural arches of the vertebrae.

Disorders of neural tube formation can involve defects in primary neurulation, closure of the anterior or posterior neuropore, or failure in the development of the lower spinal cord, which may be present before 28 days of gestation. This leads to defects in the spinal cord, dura, meninges, cranium, and vertebrae as well as the dermal coverings. Open neural tube defects, the most common being the myelomeningocele,

### CASE AT A GLANCE

#### Basic Findings

Length	: 49 cm (25th centile)
Weight	: 3 kg (25th centile)
Temperature	: 37°C
Pulse rate	: 136 per minute
Respiratory rate	: 28 per minute
Blood pressure	: 50/30 mm Hg

#### Positive Findings

##### History

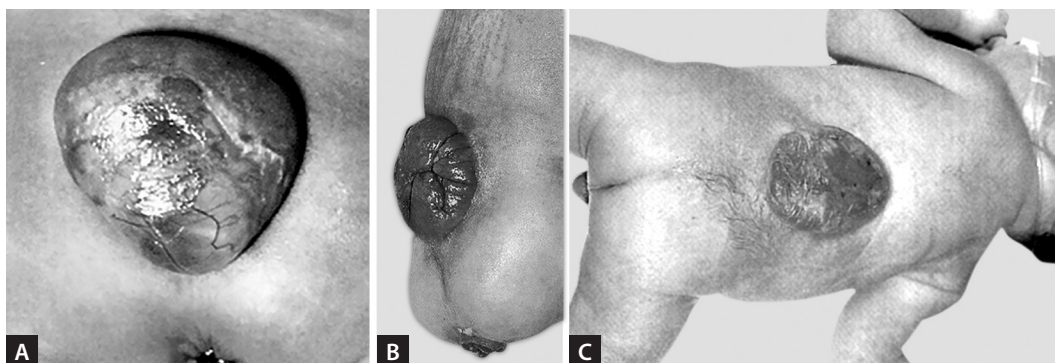
- Small swelling at lower back
- Transient tachypnea
- Breech presentation

##### Examination

- Small midline defect

##### Investigation

- Nicotinamide adenine dinucleotide (NAD)



**Figs. 1A to C:** (A and B) Meningomyelocele; (C) Myelomeningocele.  
(For color version see Plate 2)

are characterized by failure of the surface ectoderm to close over the neural elements leaving meninges and spinal cord exposed.

However, disorders in neural tube formation include a wide array of disorders including cranioschisis (total failure of neurulation), anencephaly (defects in cranial neural tissue development), and encephalocele (herniation of brain or meninges through a cranial defect), as well as occult spinal dysraphisms (skin-covered defects of vertebrae and dermal structures with subtle or absent neural abnormalities).

The defect is usually covered by transparent membrane. This may have neural tissue attached to the inner surface. Cerebrospinal fluid (CSF) leaks from this membrane initially. But soon after the birth, drying of the membrane prevents it. As the CSF accumulates membrane bulges. This eventually forms large sac.

Neural tube defects result from a combination of environmental risk factors in addition to genetic causes. About 70–80% of all cases are the result of environmental/gene interactions, with the rest being related to aneuploidies, duplications, or deletions. The most common risk factors include folic acid deficiency, fetal exposure to drugs such as valproic acid, and gestational diabetes.

Myelomeningocele represents the most severe form of dysraphism, i.e., called aperta or open form, involving the vertebral column and spinal cord, which occurs with an incidence of approximately 1 in 4000 live births.

Folate coenzymes are involved in DNA synthesis, purine synthesis, generation of formate into the formate pool, and amino acid interconversion; the conservation of homocysteine to methionine provides methionine for the synthesis of S-adenosylmethionine (SAME, an agent important

for in vivo methylation). Mutations in the genes encoding the enzymes involved in homocysteine metabolism may play a role in the pathogenesis of meningocele. These enzymes include 5, 10 methylenetetrahydrofolate reductase, cystathionine beta-synthase, and methionine synthase.

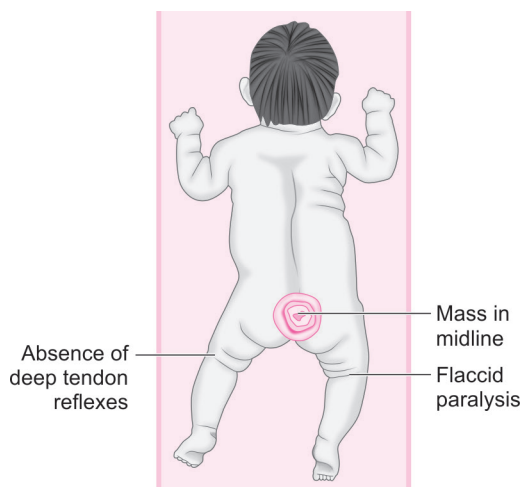
Children will have a complex multifaceted congenital disorder of structure that represents dysraphic state (a defective closure of the embryonic neural groove). It is characterized anatomically as follows:

- Presence of unfused or excessively separated vertebral arches of the bony spine
- Cystic dilation of the meninges that surround the spinal cord
- Cystic dilation of spinal cord itself
- Hydrocephalus and the spectrum of congenital cerebral abnormalities

## CLINICAL FEATURES (FIG. 2)

Myelomeningocele produces dysfunction of many organs and structures, including the skeleton, skin, and gastrointestinal and genitourinary tracts, in addition to the peripheral nervous system and the central nervous system (CNS). A myelomeningocele may be located anywhere along the neuraxis, but the lumbosacral region accounts for at least 75% of the cases. The extent and degree of the neurologic deficit depend on the location of the myelomeningocele and the associated lesions. A lesion in the low sacral region causes bowel and bladder incontinence associated with anesthesia in the perineal area but with no impairment of motor function. Newborns with a defect in the midlumbar or high lumbothoracic region typically have either a sac-like cystic structure covered by a thin layer of partially epithelialized tissue or an





**Fig. 2:** Clinical features.

exposed flat neural placode without overlying tissues. When a cyst or membrane is present, remnants of neural tissue are visible beneath the membrane, which occasionally ruptures and leaks CSF.

Infants with myelomeningocele typically have increased neurologic deficit as the myelomeningocele extends higher into the thoracic region. These infants sometimes have an associated kyphotic gibbus that requires neonatal orthopedic correction. Patients with a myelomeningocele in the upper thoracic or cervical region usually have a very minimal neurologic deficit and, in most cases, do not have hydrocephalus. They can have neurogenic bladder and bowel.

In most (80%) of the cases, meningomyelocele is associated with a type II Arnold-Chiari malformation. There will be maldevelopment and downward displacement of the cerebellum, 4th ventricle, and medulla oblongata. Hydrocephalus occurs as a result of aqueductal stenosis. The associated deformities of the meningo-myelocele include dislocated hips, talipes equinovarus and atrophy of the tongue.

Examination of the infant shows a flaccid paralysis of the lower extremities, an absence of deep tendon reflexes, a lack of response to touch and pain, and a high incidence of lower-extremity deformities (clubfeet, ankle and/or knee contractures, and subluxation of the hips). Some children have constant urinary dribbling and a relaxed anal sphincter. Other children do not leak urine and in fact have a high-pressure bladder and sphincter dyssynergy, thus, myelomeningocele above the midlumbar region tends to produce

lower motor neuron signs because of abnormalities and disruption of the conus medullaris and above spinal cord structures.

Neurological assessment should be done. This is to determine the severity of the functional defect. Pin prick over the legs and trunk will help to know the upper level of the spinal cord dysfunction. Defective innervation of the bladder is indicated by urinary dribbling. Patulous anal sphincter and lack of anal reflex indicate defective perianal region. The denervated limbs are patulous.

Diagnosis of open neural tube defects is suspected early in the second trimester of pregnancy if elevated serum levels of alpha-fetoprotein are detected. Open neural tube defects are also diagnosed prenatally through the routine use of fetal ultrasonography. Changes in the head shape (lemon sign) and cerebellum (banana sign) are often the presenting findings on fetal ultrasound. Early prenatal diagnosis is crucial in order to allow families the opportunity to plan the pregnancy, including considering the option of fetal surgery, which can be performed between 19 and 26 weeks of gestation. Prenatal diagnosis is also beneficial in order to plan for delivery at an institution.

#### GENERAL FEATURES

- Bladder incontinence
- Congenital midline defect
- Lack of response to touch and pain

#### DIFFERENTIAL DIAGNOSIS

- Spina bifida occulta
- Meningocele
- Encephalocele

#### TREATMENT

Management and supervision of a child and family with a myelomeningocele require a multidisciplinary team approach, including surgeons, other physicians, and therapists, with one individual (often a pediatrician) acting as the advocate and coordinator of the treatment program.

Postnatal treatment remains the safest treatment option for both mother and child with open neural tube defects. Infants are usually delivered at term by cesarean section to prevent potential injury to the exposed neural elements during a vaginal birth. Broad-spectrum antibiotics are started after delivery, a moist sterile dressing is applied to the back, and baseline neurologic assessment and head ultrasound are performed.

Surgery is often done within a day or so of birth but can be delayed for several days (except when

there is a CSF leak) to allow the parents time to begin to adjust to the shock and to prepare for the multiple procedures and inevitable problems that lie ahead. Evaluation of other congenital anomalies and renal function can also be initiated before surgery. Most pediatric centers aggressively treat the majority of infants with myelomeningocele. After repair of myelomeningocele, most infants require a shunting procedure for hydrocephalus. If symptoms or signs of hindbrain dysfunction appear, early surgical decompression of the posterior fossa is indicated. Clubfeet can require taping or casting, and dislocated hips may require operative procedures.

## Hydrocephalus

Open neural tube defects are one of the most common causes of pediatric hydrocephalus in the world. Prior to the introduction of fetal surgery, approximately 80% of patients with a myelomeningocele required treatment for hydrocephalus, and the most common treatment is the implantation of a CSF ventriculoperitoneal shunt. Shunts are an effective treatment; however, they have a very high failure rate, especially in infants, in whom the failure rate is 30% in the 1st year. Endoscopic third ventriculostomy with choroid plexus coagulation is a reemerging alternative treatment for hydrocephalus that does not rely on an implant and has a moderate success rate in the myelomeningocele population.

## Chiari II Malformations

Open neural tube defects usually result in Chiari II malformations. It is defined by the caudal herniation of the cerebellar vermis, brainstem, and 4th ventricle into the spinal canal, and it is associated with a variety of other changes in the brain and skull due to the persistent leak of CSF through the open neural tube defect. Most Chiari II malformations are asymptomatic or mildly symptomatic and respond to treatment with a CSF shunt. This is the leading cause of death in patients following treatment for a myelodysplastic syndrome. Treatment for this condition includes tracheostomy, gastric tube, and cervical decompressive laminectomies for palliation.

## Cognitive Development

The brain development of children with myelomeningocele is affected by the presence of the Chiari II malformation. Cognition can be further affected by complications of hydrocephalus and

by shunt infections, especially those that occur during infancy. Most individuals with myelomeningoceles have cognition in the normal range but with averages of first standard deviation below the general population. Early intervention is crucial in the 1st year of life. Therapeutic goals are best integrated into the family routine.

## Lower Extremity Paraparesis

Lower extremity weakness occurs in varying degrees with neural tube defects, and is much more common with open defects. Infants with the ability to flex their hips and extend their knees have the best prognosis for ambulation with or without orthotics. Early evaluation and intervention by a physical medicine and rehabilitation specialist maximizes the potential for ambulation.

## Neurogenic Bowel and Bladder

Neurogenic bowel and bladder leads to incontinence in nearly all individuals with open neural tube defects. Bowel and bladder dysfunction is related to the lack of communication of the lower sacral nerves with the central nervous system. Bladder pressures are often high secondary to bladder sphincter dysfunction, and poor drainage leads to stasis and risk of infection. Lack of proper bladder care can lead to the deterioration of the upper urinary tract and the development of renal disease.

Careful evaluation and reassessment of the genitourinary system are some of the most important components of the management. Periodic urine cultures and assessment of renal function including serum electrolytes and creatinine as well as renal vesico-urethrogram, renal ultrasonography, and cystometrograms are obtained according to the risk status and progress of the patient and the results of the physical examinations.

Although incontinence of fecal matter is common and is socially, unacceptable during the school years, it does not pose the same organ damaging risks as urinary dysfunction.

Management of the neurogenic bladder involves routine clean intermittent catheterization to drain the bladder and the use of anticholinergic drugs to decrease bladder irritability and pressures. Antibiotic prophylaxis is also helpful for those with vesicoureteral reflux. These treatment modalities also help with the achievement of continence.

The neurogenic bowel presents with poor motility and sphincter control, leading to incontinence. Constipation and fecal impaction are common.

Fecal impaction can lead to encopresis, with the passage of liquid stools, which is often misinterpreted by patients and their families as diarrhea. Management of the bowel involves the use of laxatives and a high-fiber diet to prevent constipation. Continence is best achieved using suppositories or enemas daily.

### Orthopedic Issues

Joint and spine complications are common such as scoliosis, talipes equinovarus, hip dislocation, and contractures. Paralysis with resulting unbalanced muscle strength around joints leads to various deformities. Management involves maximizing the potential for ambulation and independence. Scoliosis is common in higher-level lesions, but rapidly progressing curves warrant an evaluation for a tethered cord. Surgical intervention is also directed at maintenance of proper positioning in braces and wheelchairs to prevent skin break down and pressure ulcer development.

### PROGNOSIS

For the child born with defect treated aggressively, mortality rate is approximately 10–15% and death occurs before the age of 1–4 years. About 70% of survivors have normal intelligence.

Because myelomeningocele is a chronic disabling condition, periodic and consistent multidisciplinary follow-up is required for life. Renal dysfunction is one of the most important determinants of mortality.

Prognosis depends upon the extent of motor deficits and status of bladder innervation, and also associated cerebral anomalies. Most infants die during early childhood from complications of therapy such as hydrocephalus and chronic renal failure. Without surgery 90% of the affected infants die in their 1st year.

### PREVENTION

Although there have been many advancements in the care for patients with spina bifida over the years, none are as effective as prevention. Neural tube defects are not completely preventable; however, the addition of folic acid to the food supply has lowered the incidence of spina bifida significantly. Women of childbearing age should take folic acid supplementation to prevent open neural tube defects; mothers of children with spina bifida should take high doses of folic acid if they plan on becoming pregnant again. Current recommendations are 400 µg of folic acid daily for all women of childbearing ages and 4 mg daily for women who have had a previously affected pregnancy.

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# Ambiguous Genitalia

## PRESENTING COMPLAINTS

A newborn baby was brought with the complaint of abnormality in external genitalia since birth.

## History of Presenting Complaints

A baby was noticed at birth to be having ambiguous genitalia. The baby was the first child of nonconsanguineous marriage. Age of the mother was 24 years and the age of the father was 27 years. Child was born at full term by normal delivery. Mother did not have any antenatal checkup. She was not on any medication throughout the pregnancy. She went into labor spontaneously. She delivered about 12 hours of labor. The child cried immediately after the delivery. Child did not require any resuscitation. There was no family history of ambiguous genitalia.

## EXAMINATION

On examination the child was active, alert and normally built. There was no dysmorphic facial features. The color of the baby was pink. Anthropometric measurements included, the length of the child was 50 cm (50th centile), the weight of the child was 3 kg (50th centile), and the head circumference was 3 cm.

The child was afebrile. The pulse rate was 120 per minute. The respiratory rate was 30 per minute. The blood pressure recorded was 60/40 mm Hg.

There was pallor, no cyanosis and no lymphadenopathy. There was no edema and no icterus. Per abdomen examination revealed soft abdomen, liver was palpable about 2 cm below the costal margin. The baby had small phallus, perineal hypospadias and labia were fused. Two symmetrical gonads about 1 cm were palpable in the labioscrotal folds.

## CASE AT A GLANCE

### Basic Findings

Length	: 50 cm (50th centile)
Weight	: 3 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 120 per minute
Respiratory rate	: 30 per minute
Blood pressure	: 60/40 mm Hg

### Positive Findings

#### History

- Ambiguous genitalia

#### Examination

- Hepatomegaly
- Small phallus
- Perineal hypospadias
- Labia fused
- Palpable symmetric gonads

#### Investigation

- Hemoglobin: Decreased
- Serum cortisol: Increased
- 17-hydroxyprogesterone: Raised
- Urinary 17-ketosteroids: Raised
- Karyotype: 46,XY

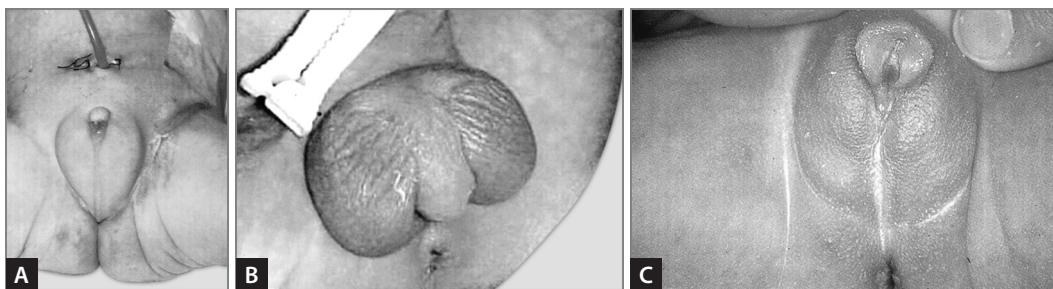
## INVESTIGATION

Hemoglobin	: 9 mg/dL
TLC	: 9,000 cells/cu mm
Serum electrolytes	: Na—140 mEq/L K—5 mEq/L Cl—100 mEq/L
Serum glucose	: 80 mg/dL
Serum cortisol	: 30 µg/dL: 8 AM 20 µg/dL: 6 PM
17-Hydroxy progesterone	: 5 nmol/L
Karyotype	: 46,XY
Urinary 17-ketosteroid	: 40 mg/24 h

## DISCUSSION

Ambiguous genitalia is defined as a discrepancy between external genitalia and internal gonads.

The definition of atypical or ambiguous genitalia, in a broad sense, in any case in which the external genitalia do not appear completely male or completely female. Although there are standards for genital size dimensions, variations



**Figs. 1A to C:** (A and B) Ambiguous genitalia; (C) Abnormal genitalia—CAH.

in size of these structures do not always constitute ambiguity.

An understanding of embryology of sexual differentiation is essential for investigation of sexual ambiguity. The sex determining region of the human Y chromosome during critical phase determines the differentiation of germinal ridge between 7 and 8 weeks of gestation. The resultant testicular tissue contains seminiferous and Sertoli cells. This produces müllerian inhibiting factor. Functional ovaries are not required for female internal genital organs.

Because there is no müllerian inhibitory substance (MIS) the gonads are ovaries and not testes, the uterus, tubes and ovaries develop. It results from the exposure of the female fetus to excessive exogenous and endogenous androgens during intrauterine life. The changes consist principally of virilization of the external genitals, i.e., clitoral hypertrophy and labioscrotal fusion. The causes are congenital adrenal hyperplasia, aromatase deficiency, virilizing maternal tumors, and administration of androgenic drugs to women during pregnancy.

A variety of abnormalities in chromosomal distribution, gonadal differentiation, gonadal function, testosterone synthesis and action, or adrenal function can lead to aberrant development of internal and external genital structures.

Antimüllerian hormone (AMH) causes the müllerian ducts to regress; in its absence, they persist as the uterus, fallopian tubes, cervix and upper vagina. AMH activation in the testes may require the *SF-1* gene by about 8 weeks of gestation the Leydig cells of the testis begin to produce testosterone. During this critical period of male differentiation, testosterone secretion is stimulated by placental human chorionic gonadotropin (hCG) which peaks at 8–12 weeks. In the latter half of pregnancy, lower levels of testosterone are maintained by luteinizing hormone (LH) secreted by the fetal pituitary. Testosterone produced locally

initiates development of the ipsilateral Wolffian duct into the epididymis, vas deferens, and seminal vesicle.

Development of the external genitalia also requires dihydrotestosterone (DHT), the more active metabolite of testosterone. DHT is produced largely from circulating testosterone and is necessary to fuse the genital folds to form penis and scrotum. DHT is also produced via an alternative biosynthetic pathway from androstanediol, and this pathway must be intact for normal and complete prenatal virilization to occur. A functional androgen receptor, produced by an X-linked gene, is required for testosterone and DHT to induce these androgen effects.

In the XX fetus with normal long and short arms of the X chromosome, the bipotential gonad develops into an ovary by about the 10th–11th week. This occurs only in the absence of SRY, testosterone and AMH and requires a normal gene in the dosage sensitive.

A female external phenotype (**Figs. 1A to C**) develops in the absence of fetal gonads. However, the male phenotype development requires androgen production and action. Estrogen is unnecessary for normal prenatal sexual differentiation, as demonstrated by 46,XX patients with aromatase deficiency and by mice without estradiol receptors.

### Abnormalities in Normal Gonadal Differentiation

These abnormalities usually result from an abnormality in the number of sex chromosomes. Klinefelter syndrome with a 47,XXY karyotype, is associated with a male phenotype but with poorly functioning testes. Turner syndrome with a 45,XO karyotype is associated with a female phenotype but with streak ovaries (gonadal dysgenesis).

Mosaic forms of gonadal dysgenesis that contain a Y-bearing cell line have variable ambiguous internal and external phenotypes.



Idiopathic testicular failure prior to completion of sexual differentiation results in ambiguous genitalia (incomplete virilization).

True hermaphroditism with the presence of both testicular and ovarian tissue, is rare and associated with external genitalia that range from fully masculine to almost completely feminine.

## Abnormalities in Testosterone Synthesis or Action

These disorders generally present as micropenis, genital ambiguity or complete absence of male external genitalia in an XY individual. Testicular tissue is present and therefore, internal structures are Wolffian.

Disorders in this category include enzymatic defects in testosterone synthesis (such as 12-ketoreductase deficiency) or defects in conversion of testosterone to DHT (5-alpha reductase deficiency). Since the gonads and adrenal gland share common enzymes of steroid hormone production, some of the enzymatic defects associated with male genital ambiguity may also affect production of cortisol and aldosterone, leading to symptoms of congenital adrenal hyperplasia or salt wasting.

Defects in testosterone action result from absent or defective androgen receptors (androgen insensitivity) and depending on the resultant degree of defect in androgen binding, the genital phenotype can range from relatively mild male ambiguity to complete female external development.

## Disorders of Adrenal Androgen Production

These disorders can cause genital ambiguity in both XY and XX individuals. Excessive adrenal androgen production secondary to an enzyme defect in cortisol synthesis (i.e., congenital adrenal hyperplasia) is the cause of 95% of inappropriate virilization in 46,XX newborns. It is a rare cause of genital ambiguity in XY individuals.

## Miscellaneous

Various syndromes such as VATER, Denys-Drash, Smith-Lemli-Opitz, have a wide variety of congenital anomalies including genital ambiguity. Maternal exposure to androgens or androgen antagonists is a rare cause of genital ambiguity in newborns.

Differentiation of the urogenital sinus and external genitalia in male is dependent on

testosterone and specifically DHT in first 14 weeks. The practical implications are as follows:

- Genetic—usually signified by karyotype.
- Gonadal—testes, ovaries or incompletely differentiated gonads.
- Phenotypic—complete male differentiation being dependent on intact testosterone and MIF pathways.

*Female pseudohermaphroditism:* The genotype is XX and gonads are ovaries. The external genitalia are virilization. This occurs if there is exposure of the female fetus to androgens during sexual differentiation. This can be because of maternal medication, maternal virilization tumor—arrhenoblastoma or adrenal androgen production.

*Male pseudohermaphroditism:* The genotype XY, but external genitalia are incompletely varitized, ambiguous or complete female.

*True:* Both the ovaries and testicular tissues are present. The clinical picture resembles male or female pseudohermaphroditism. Majority of them have 46,XX karyotype.

*Partial androgen insensitivity:* This diagnosis depends upon the confirmation that tests are morphologically normal. They are capable of testosterone synthesis and that the 5 $\alpha$ -reductase step is intact. hCG stimulation with the androgen analysis in plasma and urine samples are used to assess the Leydig cell reserves and integrity of the testosterone and DHT pathways.

If no gonads had been palpable, as occurs in most cases of the ambiguous genitalia, the most likely diagnosis would have been congenital adrenal hyperplasia (CAH).

When the gonads can be found, they are invariably testes, their development may range from rudimentary to the normal. Because of process of normal virilization in the fetus is complex, there are many varieties of male hermaphroditism.

The presence of two equal gonads means, the patient is likely to be a boy with karyotype 46,XY. These will be insensitive to testosterone or impaired biosynthesis to testosterone. When the defect is complete the patient is phenotypically female, but the partial defect produces ambiguous genitalia with palpable two gonads. This is the most common cause of male pseudohermaphroditism.

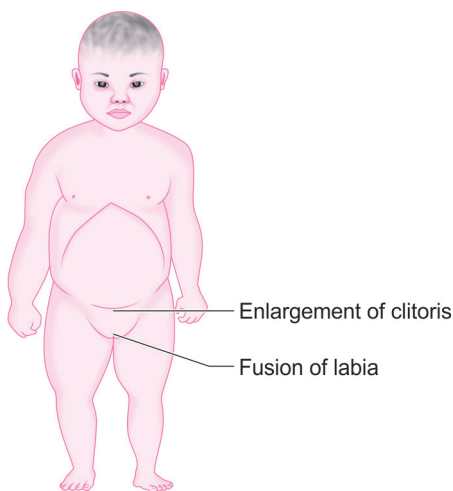
If the testosterone synthesis is impaired by an enzyme defect male informal genitalia do not develop because of lack of DHT. Gonadal biopsy is indicated to distinguish these conditions.

## CLINICAL FEATURES (FIG. 2)

There is a spectrum of characters ranging from almost complete feminization of the external genitalia to an apparently normal male with oligospermia. In more severe form, the key discussion is whether the phallus has sufficient erectile tissue to allow for growth and satisfactory male role.

A palpable gonad in the scrotum (**Fig. 3**) is nearly always testes. If no gonad is palpable and external genitalia appear ambiguous, such newborn is likely to be female with virilization due to production of excess of nongonadal androgen.

External genitalia in male child may be incompletely developed. The testes may be undescended. The genital swelling which form the scrotal fold may not fuse in the middle and superficially look like labia majora. The size of the penis may be small. This has to be differentiated from enlarged clitoris.



**Fig. 2:** Clinical features.



**Fig. 3:** Palpable gonad in the scrotum.

If the perineal urethra does not fuse, the perineal hypospadias results in female infants with ambiguous genitalia. There may be single external opening both for urethra and vagina. The presence or absence of urethra can be determined by rectal examination. Genetic abnormalities may be associated with other anomalies such as renal agenesis, anal anomalies, Wilms' tumor, aniridia, etc.

The phallus must meet two major criteria to classify as micropenis:

1. The phallus must be normally formed, with the urethral meatus located on the head of the penis and the penis positioned in an appropriate relationship to the scrotum and other pelvic structures. If these features are not present, then the term *micropenis* should be avoided.
2. The phallus must be  $>2.5$  standard deviations below the appropriate mean of age. For a term newborn, this means that a penis  $<2$  cm in a stretch length is classified as a micropenis.

It is essential that the phallus be measured appropriately. This entails the use of a rigid ruler pressed firmly against the pubic symphysis, depressing the suprapubic fat pad as possible. The phallus is grasped gently by its lateral margins and stretched. The measurement is taken along the dorsum of the penis. Note should be made of the breadth of the phallic shaft. Micropenis must be recognized early in life so that appropriate diagnostic tests can be done.

## Causes of Micropenis

Regression of the müllerian system, fusion of the labioscrotal folds and migration of the urethral meatus occur during the first trimester of gestation, further growth of the phallus during second and third trimester is dependent on production of testosterone by the response to fetal luteinizing hormone. Growth hormone also enhances penile length in utero. Thus, the following disorders can result in micropenis:

- *Hypothalamic/pituitary dysfunction:* Isolated Kallmann syndrome, Prader Willi syndrome, septo-optic dysplasia.
- *Testicular dysfunction or failure:* Intrauterine testicular torsion, testicular dysplasia.
- *Complex (testicular and/pituitary) or idiopathic:* Robinow syndrome, Klinefelter syndrome, other X polysomies.
- *Partial androgen resistance.*

## GENERAL FEATURES

- Incompletely developed genitalia
- Penis may be small
- Single external opening both for urethra and vagina

## DIAGNOSIS

The appearance of the external genitalia is rarely diagnostic of a particular disorder, and thus does not often allow distinction among the various forms of disorders of sex development. The most common forms of 46,XX disorders of sex development are virilizing forms of congenital adrenal hyperplasia. It is important to note that in 46,XY disorders of sex development, the specific diagnosis is not found in up to 50% of cases; partial androgen insensitivity syndrome and pure gonadal dysgenesis are common identifiable etiologies in XY disorders of sex development.

The six most common diagnoses accounted for 50% of the cases. These included virilizing congenital adrenal hyperplasia, androgen insensitivity syndrome, mixed gonadal dysgenesis, clitoral/labial anomalies, hypogonadotropic hypogonadism, and 46,XY small-for-gestational-age males with hypospadias.

The relative lack of established diagnoses in 46,XY disorders of sex development and the resulting lack of specific management emphasizes the need for thorough diagnostic evaluations. These include biochemical characterization of possible steroidogenic enzymatic defects in each patient with genital ambiguity. The parents need counseling about the potentially complex nature of the baby's condition, and guidance as to how to deal with their well-meaning but curious friends and family members.

The evaluation and management should be carried out by a multidisciplinary team of experts that includes pediatric endocrinology, pediatric surgery/urology, pediatric radiology, newborn medicine, genetics, and psychology. Once the sex of rearing has been agreed on by the family and team, treatment can be organized. Genetic counseling should be offered when the specific diagnosis is established.

After a complete history and physical examination, the common diagnostic approach includes multiple steps, described in the following outline. These steps are usually performed simultaneously rather than waiting for results of one test prior to performing another, because of the sensitive and sometimes urgent nature of the condition. Careful attention to the presence of physical features

other than the genitalia is crucial, to determine if a diagnosis of a particular multisystem syndrome is possible.

Diagnostic tests include the following:

- *Karyotype*, with rapid determination of sex chromosomes (in many centers this is available within 24–48 hours)
- *Other blood tests:*
  - *Screen for congenital adrenal hyperplasia:* Cortisol biosynthetic precursors and adrenal androgens (particularly 17-hydroxyprogesterone and androstenedione for 21-hydroxylase deficiency, the most common form)
  - Screen for androgens and their biosynthetic precursors
  - *Screen for gonadal response to gonadotropin in patients suspected of having testicular gonads:* Stimulation with injections of hCG; measure testosterone and DHT before and after hCG
  - Molecular genetic analyses for SRY and other Y-specific loci
  - Gonadotropin levels

Both the testosterone or estrogen estimation is useful in diagnosis of intersex states.

Human chorionic gonadotropin stimulation tests by intramuscular injection for 3–5 days helps to determine the enzymatic deficiency. Basal gonadotropin levels are elevated in primary testicular disease and androgen resistance syndrome, Turner syndrome, and gonadotropin receptor defect. The level is low in hypothalamic and pituitary defects.

Plasma testosterone/dihydrotestosterone ratio is elevated in 5- $\alpha$ -reductase deficiency. Gonadal biopsy is indicated if the karyotyping is 46,XX.

A rectal examination is done for the evaluation of presence of the vaginal pouch, uterus and prostate.

Bone age is advanced in CAH and delayed in gonadal dysgenesis and hypopituitarism.

Retrograde genitourethrogram is done to identify urogenital sinus. Pelvic ultrasonography, CT or MRI is helpful to evaluate internal genitalia, undescended gonads, and adrenal anomaly.

- *The internal anatomy* of patients with ambiguous genitalia can be defined with one or more of the following studies:
  - Voiding cystourethrogram
  - Endoscopic examination of the genitourinary tract
  - Pelvic ultrasound; renal and adrenal ultrasound

- Pelvic CT or MRI
- Exploratory laparoscopy

#### LABORATORY SALIENT FINDINGS

- Bone age
- Retrograde genitourethrogram
- Pelvic ultrasonography
- CT scan
- MRI
- *Genetic studies:* Chromosomal analysis
- Measurement of adrenal steroids
- Measurement of testosterone and dihydrotestosterone

#### ESSENTIAL DIAGNOSTIC POINTS

- Presence of gonadal structure in labioscrotal fold
- Gonads found in the inguinal canal
- Phallic size and location urethral meatus
- Presence of midline abnormalities

### DIFFERENTIAL DIAGNOSIS

- Congenital adrenal hyperplasia
- Precocious puberty
- Reifenstein's syndrome

- Leydig cell agenesis
- Tumor of adrenal

### TREATMENT

In male pseudohermaphroditism, a trial of exogenous testosterone depo injection (25 mg) monthly for 3 months can be used to judge whether there is an adequate increase in stretched penile length.

If the female role is agreed, management includes genitoplasty with reconstruction of vagina (uterus and fallopian tube are absent). Removal of testes is advised to avoid the masculinization in puberty. Estrogen replacement is introduced from age of 12 years.

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# Congenital Adrenal Hyperplasia

## PRESENTING COMPLAINTS

A 3-week-old boy was brought with the complaints of:

- Vomiting since 2 weeks
- Not taking proper feeds since 1 week

## History of Presenting Complaints

A 3-week-old boy brought to the hospital early in the morning with the history that child is not taking feeds. Mother complained that her son was not taking feeds properly and not sucking satisfactorily. Mother also told that he was vomiting. Child had several bouts of vomiting. Vomitus used to contain the milk in curdled form. He was exclusively on breast milk.

## Past History of the Patient

He was the second sibling of nonconsanguineous marriage. He was born at full term by normal delivery. He cried immediately after the delivery. The birth weight was 3.25 kg. The head circumference was 35 cm. There was no significant postnatal event. He started taking breast milk

regularly. Child was discharged on 5th day. He had transient physiological jaundice.

## EXAMINATION

On examination, the child was moderately built and nourished. There were signs of moderate dehydration. Anterior fontanelle was sunken. He was lying flaccid on the examination table. Anthropometric measurements included, length was 54 cm (75th centile), the weight was 3 kg (10th centile), and head circumference was 35 cm.

The child was afebrile. The pulse rate was 116 per minute and respiratory rate was 30 per minute. Blood pressure recorded was 60/50 mm Hg. Pallor was present. No edema, no icterus, and no lymphadenopathy. Per abdomen revealed presence of mild distension. There was no organomegaly and other systemic examinations were normal.

## INVESTIGATIONS

Hemoglobin	: 10 g/dL
TLC	: 7,000 cells/cu mm
ESR	: 22 mm in the 1st hour
Blood urea	: 16 mg/dL
Plasma testosterone	: 15 nmol (Normal range: 9.5–30 nmol/L)
Plasma cortisol	: 6 µg/dL at 8 AM 2 µg/dL at 6 PM
Serum aldosterone	: 5 ng/dL
Serum electrolyte	: Na—118 mEq/L K—4 mEq/L HCO <sub>3</sub> —12 mEq/L

Plasma 17-hydroxyprogesterone	: 650 nmol/L
Urine routine	: Normal
Hydrocortisone challenge test for urinary 17-hydroxyprogesterone	: 488 nmol (Normal range: <15 nmol)
Ultrasound abdomen	: To rule out hydro-nephrosis and bladder obstruction

### CASE AT A GLANCE

#### Basic Findings

Length	: 54 cm (75th centile)
Weight	: 3 kg (10th centile)
Temperature	: 37°C
Pulse rate	: 116 per minute
Respiratory rate	: 30 per minute
Blood pressure	: 60/50 mm Hg

#### Positive Findings

##### History

- Feeding problems
- Vomiting

##### Examination

- Dehydration

##### Investigation

- Hyponatremia
- Hyperkalemia
- Hydrocortisone challenge test: Increased 17-hydroxyprogesterone levels



## DISCUSSION

A 3-week-old boy presented with history of feeding problems and persistent vomiting with severe dehydration. This is also associated with hyponatremia and hyperkalemia with raised 17-hydroxy-progesterone levels. These findings suggest congenital adrenal hyperplasia.

It is inherited as autosomal recessive trait. It is a group of defects in steroid synthesis, is characterized by deficiency of adrenocortical hormones on one hand and excess of steroid precursors on the other hand. As most steroidogenic enzymes are expressed in the adrenal, their disorders tend to be lumped under the term congenital adrenal hyperplasia (CAH).

Most disorders of adrenal steroidogenesis are not characterized by adrenal hyperplasia. One form of CAH, 21-hydroxylase deficiency (21-OHD), accounts for >90% of cases and is found in all ethnic groups. The other disorders are rare and tend to be found in isolated genetic clusters. Because each steroidogenic enzyme has multiple activities and many extra-adrenal tissues contain enzymes that have similar activities, the complete elimination of a specific adrenal enzyme may not result in the complete elimination of its steroidal products from the circulation.

Five distinct varieties have been identified:

1. 21-hydroxylase deficiency
2. 11-hydroxylase deficiency
3. 3-beta-hydroxysteroid dehydrogenase deficiency
4. 20-22 desmolase deficiency
5. 17-hydroxylase deficiency

Congenital adrenal hyperplasia is due to the defects in enzymatic sequence and converts cholesterol to cortisol, aldosterone and sex steroids. These defects may manifest as:

- Masculinization of female
- Under masculinization of male
- Acute crisis in salt losing type
- Failure to thrive
- Hypertension
- Postnatal virilization with growth acceleration

Autosomal recessive enzyme defects involved in adrenal steroidogenesis are common. Defect in cortisol biosynthesis with resultant increased adrenocorticotrophic hormone (ACTH) secretion occurs during fetal life. ACTH excess subsequently results in adrenal hyperplasia with increased production of various adrenal hormone precursors, including androgens and increased urinary excretion of their metabolites. Increased pigmentation,

especially of the scrotum, labia majora and nipples frequently results from excessive ACTH secretion.

Often there is a family history of unexplained death in infancy. Female newborn infants show virilization of external genitalia resulting from 11 or 21-hydroxylase deficiency. In its severe form, excess adrenal androgen production beginning in the first trimester of the fetal development results in virilization of the female infant and life-threatening hypovolemic, hyponatremic shock (adrenal crisis) in the newborn.

Patients with 21-hydroxylase deficiency indicate that the clinical type (salt-wasting versus non-salt wasting) is usually consistent within a family and that a close genetic linkage exists between the 21-hydroxylase gene and the HLA complex on chromosome 6.

The diagnosis of 21-hydroxylase deficiency (21-OHD) is suggested by genital ambiguity in females, a salt-losing episode in either sex, or rapid growth and virilization in males or females. Plasma 17-hydroxyprogesterone (17-OHP) is markedly elevated (>2,000 ng/dL after 24 hours of age in an otherwise healthy full-term infant) and hyper-responsive to stimulation with ACTH. Additional measurement of 11-deoxycortisol, 17-OHP, dehydroepiandrosterone (DHEA), and androstenedione distinguishes among the forms of CAH and testicular tumors that also produce 17-HP. Similarly, ACTH will induce a substantial rise in serum 21-deoxycortisol in all forms of 21-OHP, but not in normals, providing a useful adjunctive test when this steroid can be measured.

Female pseudohermaphroditism can be caused by factors other than enzyme deficiencies. These factors include virilizing maternal conditions or related hormones taken by the mother during the first trimester of pregnancy. In such cases, the condition does not progress after birth, and cortisol deficiency with abnormal steroidogenesis is not present.

Male pseudohermaphroditism may occur in children with 17,20-desmolase deficiency because that enzyme is necessary for normal androgen biosynthesis. Male pseudohermaphroditism can also be a consequence of androgen receptor abnormalities.

Virilization of the female or male fetus may result from tumors of the adrenal gland, ovary or testes or from nonclassic congenital adrenal hyperplasia later in life. Symptoms begin after birth and progress until treated.

Congenital adrenal hyperplasia is usually classified as part of a spectrum of three typical

presentations that result from varying degrees of enzyme activity.

### Salt-wasting CAH

More than 90% of CAH cases are caused by 21-hydroxylase deficiency. This P450 enzyme (CYP21, P450c21) hydroxylates progesterone and 17-hydroxyprogesterone to yield 11-deoxycorticosterone and 11-deoxycortisol, respectively. These conversions are required for synthesis of aldosterone and cortisol, respectively. Both hormones are deficient in the most-severe “salt-wasting” form of the disease.

Patients with the most severe form (salt-wasting CAH) have aldosterone deficiency due to an inability to convert progesterone to deoxycorticosterone (DOC). This results in severe hyponatremia (Na often  $<110$  mEq/L), hyperkalemia (K often  $>10$  mEq/L), and acidosis (pH often  $<7.1$ ) with concomitant hypotension, shock, cardiovascular collapse, and death in an untreated newborn infant; this usually develops during the 2nd week of life.

Cortisol deficiency results from the inability to convert 17-OHP to 11-deoxycortisol. This impairs postnatal carbohydrate metabolism and worsens cardiovascular collapse because a permissive action of cortisol is required for full pressure action of catecholamines. Low fetal cortisol stimulates corticotropin (ACTH) secretion, which stimulates adrenal growth and stimulates the steroidogenic steps upstream, leading to accumulation of 17-OHP and other steroids that can be converted to testosterone.

Affected females are often diagnosed at birth because of genital virilization. Males are undiagnosed at birth and either come to medical attention due to screening or during a salt-losing crisis, typically in the 2nd week of life. Following initial fluid and electrolyte resuscitation, the mineralocorticoids and glucocorticoids can be replaced orally and the genital virilization can be corrected surgically. Drug doses require frequent adjustment in the growing child, and there is also considerable individual variability in what constitutes physiologic replacement.

### Simple Virilizing CAH

Slightly less-severely affected patients are able to synthesize adequate amounts of aldosterone but have elevated levels of androgens of adrenal origin; this is termed “simple virilizing disease”.

Virilized females with elevated 17-OHP concentrations who do not suffer a salt-losing crisis

have the “simple virilizing” form of CAH. Males with this disorder often escape diagnosis until ages 3–7 years, when they come to medical attention because of early development of pubic, axillary, and facial hair, and phallic growth. In contrast to boys with true central precocious puberty, when sexual precocity is caused by CAH, the testes remain of prepubertal size because they have not been stimulated by gonadotropins. These children grow rapidly and are tall for age when diagnosed, but their bone ages are advanced, so that their ultimate adult height is invariably compromised.

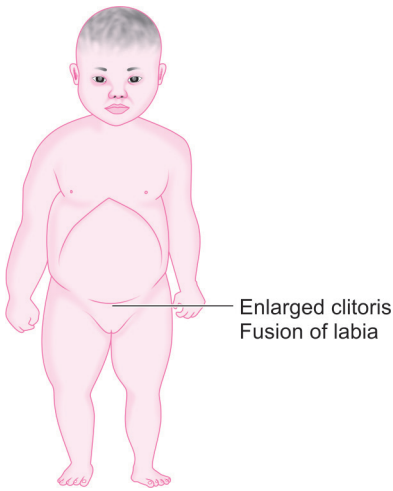
When treatment is begun at several years of age, suppression of adrenal testosterone secretion may remove tonic inhibition of the hypothalamus, occasionally resulting in true central precocious puberty, requiring treatment with a gonadotropin-releasing hormone (GnRH) agonist. High concentrations of ACTH in some poorly treated boys may stimulate the enlargement of adrenal rests in the testes. These enlarged testes are usually nodular, unlike the homogeneously enlarged testes in central precocious puberty. Because the adrenal normally produces 100 to 1,000 times as much cortisol as aldosterone, mild defects in P450c21 are less likely to affect mineralocorticoid secretion than cortisol secretion. Thus, patients with simple virilizing CAH simply have a less severe disorder of P450c21. This is reflected physiologically by the increased plasma renin activity seen in these patients after moderate salt restriction.

### Nonclassic CAH

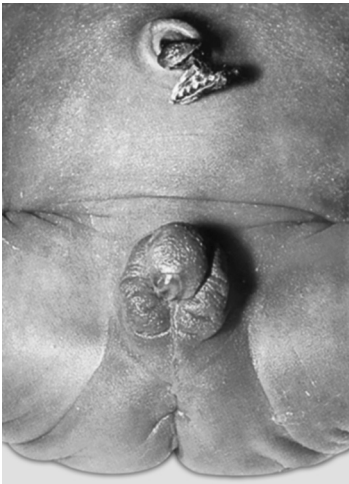
Patients with nonclassic disease have relatively mildly elevated levels of androgens and may be asymptomatic or have signs of androgen excess at any time after birth. Very mild forms of CAH are common, evidenced by hirsutism, virilism, menstrual irregularities, and decreased fertility in adult women (so-called late-onset CAH). However, sometimes there may be no phenotypic manifestations other than an increased response of plasma 17-OHP to an intravenous ACTH test.

### CLINICAL FEATURES (FIG. 1)

- *In females:* In the female with potentially normal ovaries and uterus, virilization occurs and sexual development is therefore along heterosexual lines. The abnormality of the external genitalia may vary from mild enlargement of the clitoris to complete fusion of the labioscrotal folds, forming a scrotum, a penile urethra, a penile shaft, and enlargement



**Fig. 1:** Clinical features.



**Fig. 2:** Congenital adrenal hyperplasia.  
(For color version see Plate 3)

of the clitoris to form a normal-sized glans (**Fig. 2**).

It is associated with some degree of masculinization at birth. It is expressed as enlarged clitoris and varying degree of labial fusion. The vagina has a common opening with urethra. The internal genital organs are those of normal female. The severity of virilization is greater in salt-losing CAH.

Signs of adrenal insufficiency (salt loss) may be present during the first few days of life (typically in the 1st or 2nd week). In rare cases, adrenal insufficiency does not occur for months or years. When the enzyme defect is milder, salt loss may not occur and evidence

of virilization predominates (simple virilizing form).

In untreated, non-salt-losing 21-hydroxylase or 11-hydroxylase deficiency, growth rate and skeletal maturation are accelerated and patients may become muscular. Pubic hair appears early (often before the 2nd year); acne may be excessive; and the voice may deepen. Excessive pigmentation may develop.

- *In males:* In males, sexual development proceeds normally. The male infant usually appears normal at birth but may present with a salt losing crisis in the first 2–4 weeks of life. In milder forms, salt-losing crisis may not occur. In this circumstance, enlargement of the penis and increased pigmentation may be noted during the first few months.

In males, there is premature isosexual development. Somatic precocity may appear within first 6 months of life and develop more gradually becoming evident at the age of 4–5 years. Enlargement of penis and scrotum, acne and deep voice are noted. Muscles are well developed and bone age is advanced for chronological age. Although affected patients are tall in early childhood, premature closure of epiphyses causes the growth to stop relatively early. Adult stature is shunted. The testes are normal in size and appear relatively smaller in proportionate to the size of the penis.

Urinary excretion of 17-ketosteroids and pregnanetriol is increased. In 21-hydroxylase deficiency, plasma 17-hydroxyprogesterone levels are increased. In 11-hydroxylase deficiency serum levels of the compounds and DOC are elevated (**Table 1**).

Other symptoms and signs are similar to those seen in females. The testes are soft and not enlarged except in the rare male in whom aberrant adrenal cells (adrenal rests) are present in the testes and produce unilateral or bilateral enlargement, often asymmetric.

In the male fetus with 21-OHD, the additional testosterone produced in the adrenals has no phenotypic effect. In a female fetus, the testosterone inappropriately produced by the adrenals of the affected female fetus causes varying degrees of virilization of the external genitalia [disordered sexual development (DSD)]. This can range from mild clitoromegaly with or without posterior fusion of the labioscrotal folds to complete labioscrotal fusion that includes a urethra traversing the enlarged clitoris. These infants

**TABLE 1:** Clinical and laboratory findings in adrenal enzyme defects resulting in congenital adrenal hyperplasia (CAH).

Enzyme deficiency	Urinary 17-ketosteroids	Elevated plasma metabolite	Plasma androgens	Aldosterone	Hyper-tension/salt loss	External genitalia
20, 22-Desmolase	↓↓↓	–	↓↓↓	↓↓↓	–/+	Males: Ambiguous Females: Normal
3β-ol-dehydro-genase	↑↑ (DHEA)	17-OH-Pregnenolone (DHEA)	↑ (DHEA)	↓↓↓	–/+	Males: Ambiguous Females: Possible virilized
17-Hydroxylase	↓↓↓	Progesterone	↓↓	↑ Normal to	+/-	Males: Ambiguous Females: Normal
21-Hydroxylase	↑↑↑	17-OHP	↑↑	↓↓	–/+	Males: Normal Females: Virilized
11-Hydroxylase	↑↑	11-Deoxy-cortisol	↑↑	↓↓ (Deoxycorti-costerone)	+/-	Males: Normal Females: Virilized
17, 20-Desmolase	↓↓↓	17-Hydro-xysteroids	↓↓	Normal	–/-	Males: Ambiguous Females: Normal

have normal ovaries, fallopian tubes, and a uterus, but their external genitalia may be sufficiently virilized so that they appear to be male, resulting in errors of sex assignment at birth.

In the rare isolated defect of 17, 20-desmolase activity, ambiguous genitalia may be present because of the compromise in androgen production.

**ESSENTIAL DIAGNOSTIC POINTS**

- Pseudohermaphroditism in females, with urogenital sinus, enlargement of clitoris, or other evidence of virilization
- Salt-losing crisis in infant males or increased precocity in older males with infantile testes
- Increased linear growth in young children, advancement of skeletal maturation
- *Urinary and plasma androgen elevation:* Plasma 17-hydroxyprogesterone and urinary pregnanetriol concentration increased

**DIAGNOSIS**

17-OHP is normally high in cord blood, but falls to normal newborn levels after 12–24 hours, thus, assessment of 17-OHP levels should not be made in the first 24 hours of life. In general, when testing is done on full-term infants more than 24 hours after birth, the screening is reliable. Pediatricians should become familiar with local assays and the values found in premature infants, which may be read as false positives for 21-OHD. Premature infants and term infants under severe stress (e.g., with cardiac or pulmonary disease) typically

have persistently elevated 17-OHP concentrations with normal 21-hydroxylase.

Diagnosis of salt-wasting form is established by demonstration of extreme elevation of 17-hydroxyprogesterone levels (10,000–20,000 ng/dL, normal <90 ng/dL) in presence of clinical and laboratory features of adrenal insufficiency. 17-hydroxyprogesterone levels are elevated to a lesser extent in those with simple virilizing and nonclassic forms.

Diagnosis of 21-hydroxylase deficiency is most reliably established by measuring 17-hydroxyprogesterone before and 30 or 60 minutes after an intravenous (IV) bolus of 0.125–0.25 mg or 0.25 mg intramuscular (IM) injection of synacthen ACTH. On short synacthen (also ACTH) stimulation test, serum 17-OHP and DHEA rise more than 2–3 folds but there is no significant elevation of serum cortisol. Basal levels are usually >2000 ng/dL and there will be increase to more than 5,000–10,000 ng/dL after ACTH in CAH. Patients with nonclassical CAH typically have normal to mildly elevated basal levels, but supranormal responses to ACTH stimulation. The cortisol response to ACTH is subnormal in patients with classical CAH and is normal in patients with nonclassical CAH.

Patients with salt-losing disease have typical laboratory findings associated with cortisol and aldosterone deficiency, including hyponatremia, hyperkalemia, metabolic acidosis, and often hypoglycemia, but these abnormalities can take 10–14 days or longer to develop after birth.

Blood levels of 17-hydroxyprogesterone are markedly elevated. However, levels of this hormone are high during the first 2–3 days of life even in unaffected infants and especially if they are sick or premature. Blood levels of cortisol are usually low in patients with the salt-losing type of disease. They are often normal in patients with simple virilizing disease but inappropriately low in relation to the ACTH and 17-hydroxyprogesterone levels.

In addition to 17-hydroxyprogesterone, levels of androstenedione and testosterone are elevated in affected females; testosterone is not elevated in affected males, because normal infant males have high testosterone levels compared with those seen later in childhood. Levels of urinary 17-ketosteroids and pregnanetriol are elevated but are now rarely used clinically because blood samples are easier to obtain than 24-hour urine collections. ACTH levels are elevated but have no diagnostic utility over 17-hydroxyprogesterone levels. Plasma levels of renin are elevated, and serum aldosterone is inappropriately low for the rennin level. However, renin levels are high in normal infants in the first few weeks of life.

- **Blood and urine:** Hormonal studies are essential for accurate diagnosis. With adrenal tumor, secretion of DHEA is greatly elevated and determining plasma concentrations of DHEA sulfate may be useful in the differential diagnosis.
- **Genetic studies:** When available, rapid chromosomal diagnosis should be obtained in any newborn with ambiguous genitalia. A buccal smear and karyotype are done to determine the gender of infants.
- **Radiograph:** Adrenal ultrasonography, CT scanning and MRI may be useful in defining pelvic anatomy or enlarged adrenals or in localizing an adrenal tumor. Vaginograms using contrast material and pelvic ultrasonography may be helpful in delineating the internal anatomy in a newborn with ambiguous genitalia.

Prenatal diagnosis can be done by estimation of 17-ketosteroids, pregnanetriol and 17-OHP in amniotic fluid or by genotyping HLA typing of amniotic cells obtained by chorion villus sampling. Neonatal screening can be performed by heel prick blood 17-OHP estimation.

#### GENERAL FEATURES

- Virilization at birth
- Children grow tall
- Failure to thrive
- Advanced bone age

#### LABORATORY SALIENT FINDINGS

- Hormonal studies
- Secretion of DHEA increased
- *Genetic studies:* Chromosomal analysis
- Adrenal ultrasonography
- CT scan
- MRI
- Pelvic ultrasonography

#### DIFFERENTIAL DIAGNOSIS

- Precocious puberty
- Pyloric stenosis
- Intestinal obstruction
- Hypothyroidism
- Virilizing tumor

#### TREATMENT

##### Medical Treatment

Treatment in congenital adrenal hyperplasia consists of normalizing growth velocity and skeletal maturation using the smallest dose of glucocorticoids that will suppress adrenal function.

- **Glucocorticoids:** Cortisol deficiency is treated with glucocorticoids. Treatment also suppresses excessive production of androgens by the adrenal cortex and thus minimizes problems such as excessive growth and skeletal maturation and virilization. This often requires larger glucocorticoid doses than are needed in other forms of adrenal insufficiency, typically 15–20 mg/m<sup>2</sup>/24 h of hydrocortisone daily administered orally in three divided doses. Affected infants usually require dosing at the high end of this range. Double or triple doses are indicated during periods of stress such as infection or surgery. Between 50 and 60% of the daily dose should be given in the late evening to suppress the early morning ACTH rise. Dosage is adjusted to maintain a normal growth rate and a normal rate of skeletal maturation.

Glucocorticoid treatment must be continued indefinitely in all patients with classic 21-hydroxylase deficiency but may not be necessary in patients with nonclassic disease unless signs of androgen excess are present. Therapy must be individualized. It is desirable to maintain linear growth along percentile lines; crossing to higher height percentiles may suggest undertreatment, whereas loss of height percentiles often indicates overtreatment with glucocorticoids. Overtreatment is also suggested by excessive weight gain.



Pubertal development should be monitored by periodic examination and skeletal maturation is evaluated by serial radiographs of the hand and wrist for bone age.

Hormone levels, particularly 17-hydroxyprogesterone and androstenedione, should be measured early in the morning, before taking the morning medications, or at a consistent time in relation to medication dosing. In general, desirable 17-hydroxyprogesterone levels are in the high-normal range or several times normal; low-normal levels can usually be achieved only with excessive glucocorticoid doses.

Menarche occurs at the appropriate age in most girls in whom good control has been achieved; it may be delayed in girls with suboptimal control.

Children with simple virilizing disease, particularly males, are frequently not diagnosed until 3–7 years of age, at which time skeletal maturation may be 5 years or more in advance of chronological age. In some children, especially if the bone age is 12 years or more, spontaneous central (i.e., gonadotropin-dependent) puberty may occur when treatment is instituted, because therapy with hydrocortisone suppresses production of adrenal androgens and thus stimulates release of pituitary gonadotropins if the appropriate level of hypothalamic maturation is present. This form of superimposed true precocious puberty may be treated with a gonadotropin hormone-releasing hormone analog such leuprolide.

Males with 21-hydroxylase deficiency who have had inadequate corticosteroid therapy may develop testicular adrenal rest tumors, which usually regress with increased steroid dosage. Testicular MRI, ultrasonography, and color flow Doppler examination help define the character and extent of disease. Testis-sparing surgery for steroid-unresponsive tumors has been reported.

A variety of serum and urine androgens have been used to monitor adequacy of therapy, including 17-hydroxyprogesterone, androstenedione and urinary pregnanetriol. In adolescent females, normal menses are a sensitive index of the adequacy of therapy.

- **Mineralocorticoids:** Fludrocortisone in a dose of 0.05–0.15 mg is given orally once a day or

in two divided doses. Periodic monitoring of blood pressure is recommended to avoid overdosing.

Patients with salt-wasting disease (i.e., aldosterone deficiency) require mineralocorticoid replacement with fludrocortisone. Infants may have very high mineralocorticoid requirements in the first few months of life, usually 0.1–0.3 mg daily in two divided doses but occasionally up to 0.4 mg daily, and often require sodium supplementation (sodium chloride, 8 mmol/kg) in addition to the mineralocorticoid.

Older patients and children are usually maintained with 0.05–0.1 mg daily of fludrocortisone. In some patients, simple virilizing disease may be easier to control with a low dose of fludrocortisone in addition to hydrocortisone even when these patients have normal aldosterone levels in the absence of mineralocorticoid replacement.

Therapy is evaluated by monitoring of vital signs; tachycardia and hypertension are signs of overtreatment with mineralocorticoids. Serum electrolytes should be measured frequently in early infancy as therapy is adjusted. Plasma renin activity is a useful way to determine adequacy of therapy; it should be maintained in or near the normal range but not suppressed.

Children with salt wasting and those with elevated plasma renin activity, require increased salt intake and mineralocorticoid. In first 24 hours of dehydration, 4–8 g of sodium chloride is needed for the replacement. In infants, 9- $\alpha$ -fluorocortisone acetate is given in the dose of 0.05–0.1 mg/day in addition.

## Surgical Treatment

Consultation with an urologist experienced with female genital reconstruction is indicated in affected females as soon as possible during infancy.

Feminizing genitoplasty is undertaken in staged manner. The enlarged clitoris is resected within the 1st year. Vaginoplasty is undertaken after sometime.

## COURSE AND PROGNOSIS

When therapy is initiated in early infancy, abnormal metabolic effects and progression of

masculinization can be avoided. Treatment with glucocorticoids permits normal growth, development and sexual maturation.

However, if not adequately controlled, congenital adrenal hyperplasia results in sexual precocity and masculinization throughout childhood. Affected individuals will be tall as children but short as adults because the rate of skeletal maturation is excessive and leads to premature closure of epiphyses.

If treatment is delayed or inadequate until somatic development is over 12–14 years as determined by skeletal maturation (bone age), true central sexual precocity may occur in males and females.

Patient education stressing lifelong therapy is important to ensure compliance in adolescence and later life.

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# Cushing Syndrome

## PRESENTING COMPLAINTS

A 10-year-old girl was presented with the complaints of:

- Fever since 3 days
- Abdominal pain since 2 days

## History of Presenting Complaints

A 10-year-old girl presented with history of abdominal pain. Abdominal pain was present on the right side of loin. According to the girl, the abdominal pain was radiating from loin to inner part of thigh. The pain was of severe type. It was associated with moderate degree of fever. Fever was of intermittent type associated with chills and rigors. There were no history suggestive urinary and bladder disturbances.

## Past History of the Patient

She was the eldest sibling of nonconsanguineous marriage. She was delivered at full term by normal

delivery. Her birth weight was 3.25 kg. She was on breastfeeds immediately after the delivery. She was exclusively on breastfeeds for first 3 months. Later weaning was started with cereals and fruits. She was on family food from 18 months. Her developmental milestones were normal. She was completely immunized. She was overweight despite of strict diet control. Her weight increased markedly in the last 6 months. The younger sibling was 6-year-old healthy boy.

## EXAMINATION

The girl was much obese. She was looking unhappy. Her anthropometric measurements included, her height was 133 cm (50th centile), her weight was 38 kg (90th centile). She was febrile, 38°C. Her pulse rate was 110 per minute, and respiratory rate was 22 per minute. Blood pressure recorded was 140/96 mm Hg.

There was no pallor, no lymphadenopathy, and no edema. The face was round with prominent cheeks. Hypertrichoses on the face was present. Acne were present. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 13 g/dL
TLC	: 16,000 cells/cu mm
AEC	: 750 cells/cu mm
Blood urea	: 40 mg/dL
Serum electrolytes	: Na—150 mEq/dL K—2.5 mEq/dL
Plasma cortisol	: 30 µg/dL at 8 AM 20 µg/dL at 6 PM
Serum androgen	: 3 nmol/L (Normal 1.08–2.26 nmol/L)
Urine routine	: 10–20 WBCs/HPF Protein ++ Red cells +++ Albumin ++
Urinary 17-hydroxycorticosteroids	: 20 mg/dL/24 h (Normal range: 2–8 mg/dL/24 h)

### CASE AT A GLANCE

#### Basic Findings

Height	: 133 cm (50th centile)
Weight	: 38 kg (90th centile)
Temperature	: 38°C
Pulse rate	: 110 per minute
Respiratory rate	: 22 per minute
Blood pressure	: 140/96 mm Hg

#### Positive Findings

##### History

- Abdominal pain
- Fever
- Obese

##### Examination

- Obese
- Prominent cheeks
- Hypertension
- Buffalo hump

##### Investigation

- Urine: Suggestive of UTI
- Plasma cortisol: Increased
- Serum androgen: Increased
- Urinary 17-hydroxycorticosteroids: Increased
- Urinary 17-ketosteroids: Increased

Urinary  
17-ketosteroids : 26 mg/dL/24 h (Normal  
range: 4–13 mg/dL/24 h)

## DISCUSSION

Girl presented with urinary tract infection, obesity, presence of acne and systemic hypertension. These clinical features make the diagnosis of Cushing syndrome.

Cushing syndrome is the result of abnormally high blood levels of cortisol or other glucocorticoids. Iatrogenic Cushing syndrome results from administration of supraphysiologic quantities of glucocorticoids. Early signs of glucocorticoid excess include increased appetite, weight gain, and growth arrest without delayed bone age.

Chronic glucocorticoid excess in children results in typical Cushingoid facies, but the centripetal fat distribution characteristic of adult Cushing disease is seen only in long-standing disease. Mineralocorticoid excess is characterized by hypertension, but patients receiving low-sodium diets (e.g., newborns) are not hypertensive, as mineralocorticoids increase blood pressure by retaining sodium and increasing intravascular volume.

Moderate hypersecretion of adrenal androgens is characterized by mild signs of virilization; substantial hypersecretion of adrenal androgens is characterized by accelerated growth, increased bone age, increased muscle mass, acne, hirsutism, and deepening of the voice.

Cushing disease designates hypercortisolism from pituitary, over-production of corticotropin (ACTH). Other causes include adrenal adenoma, adrenal carcinoma, multinodular adrenal hyperplasias, and the ectopic adrenocorticotrophic hormone (ACTH) syndrome.

## ETIOLOGY

Cushing syndrome is nonspecific. It may result from excessive secretion of adrenal steroids autonomously (adenoma or carcinoma), from excessive ACTH secretion from the pituitary (Cushing disease) or from ectopic sources, or from chronic exposure to pharmacologic doses of glucocorticoids. ACTH independent Cushing syndrome with nodular hyperplasia and adenoma formation occur in cases of McCune–Albright syndrome. The symptoms begin in infancy and childhood.

In children under age 12 years, Cushing syndrome is usually iatrogenic (secondary to pharmacologic doses of ACTH or one of the glucocorticoids). It may rarely be due to an adrenal

tumor, adrenal hyperplasia, an adenoma of the pituitary gland, or even more rarely, an extra-pituitary (ectopic) ACTH producing tumor from bronchus, thymus and pancreas.

The most common cause of Cushing syndrome is prolonged exogenous administration of glucocorticoid hormones, especially at the high doses used to treat lymphoproliferative disorders. This rarely represents a diagnostic challenge, but management of hyperglycemia, hypertension, weight gain, linear growth retardation, and osteoporosis often complicates therapy with corticosteroids.

The most common etiology of endogenous Cushing syndrome in children older than 7 years of age is Cushing disease, in which excessive ACTH secreted by a pituitary adenoma causes bilateral adrenal hyperplasia. Patients with these tumors often exhibit signs of hypercortisolism along with signs of hypersecretion of other steroids such as androgens, estrogens, and aldosterone. Such adenomas are often too small to detect by imaging techniques and are termed microadenomas. They consist principally of chromophobe cells and frequently show positive immunostaining for ACTH and its precursor, pro-opiomelanocortin.

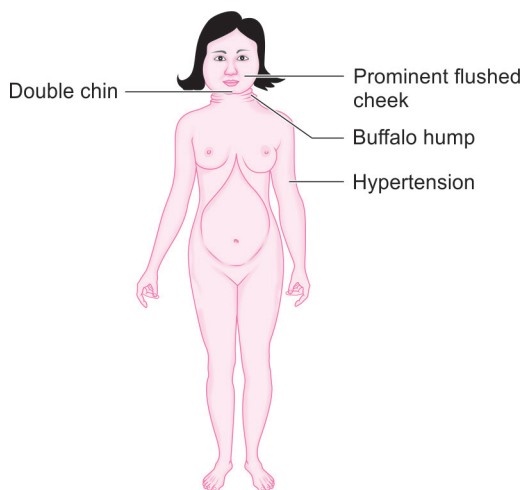
Adrenocorticotrophic hormone-dependent Cushing syndrome may also result from ectopic production of ACTH, although this is uncommon in children. Ectopic ACTH secretion in children is associated with islet cell carcinoma of the pancreas, neuroblastoma or ganglioneuroblastoma, hemangiopericytoma, Wilms tumor, and thymic carcinoid. Hypertension is more common in the ectopic ACTH syndrome than in other forms of Cushing syndrome, because very high cortisol levels.

Adrenocorticotrophic hormone-independent Cushing syndrome with nodular hyperplasia and adenoma formation occurs rarely in cases of McCune–Albright syndrome, with symptoms beginning in infancy or childhood.

## CLINICAL FEATURES (FIG. 1)

Cushing syndrome is characterized by obesity with associated hypertension. It occurs as a result of maintenance of abnormally high blood levels of cortisol by hyperfunction of adrenal cortex. In infants, it is most commonly caused by functioning adrenocortical tumor. Primary pigmented nodular adrenocortical disease is also the cause among infants and children. In children above 7 years bilateral adrenal hyperplasia is the cause. It may be because of ectopic production of ACTH.

Signs of Cushing syndrome have been recognized in infant younger than 1 year of age.



**Fig. 1:** Clinical features.

The disorder appears to be more severe and the clinical findings more flagrant in infants than in older children. The face is rounded, with prominent cheeks and a flushed appearance (moon facies). Generalized obesity is common in younger children. In children with adrenal tumors, signs of abnormal masculinization occur frequently; accordingly, there may be hirsutism on the face and trunk to pubic hair, acne, deepening of the voice, and enlargement of the clitoris in girls. Growth is impaired, with length falling below the 3rd percentile, except when significant virilization produces normal or even accelerated growth. Hypertension is common and may occasionally lead to heart failure. An increased susceptibility to infection may also lead to sepsis.

#### ESSENTIAL DIAGNOSTIC POINTS

- Truncal adiposity with thin extremities.
- Moon facies, muscle wasting, weakness, plethora.
- Easy bruising, purplish striae, decreased growth rate, delayed skeletal maturation.
- Hypertension, osteoporosis, glycosuria.
- Elevated serum and urine adrenocorticosteroids; low serum potassium levels; eosinopenia, lymphopenia.

Prolonged exogenous administration of corticotropin or hydrocortisone or its analog results in clinical pattern. Clinical manifestations are due to gluconeogenesis, which leads to protein catabolism and accumulation of fat. These children have rounded face with the prominent flushed cheeks and double chins, i.e., moon facies. Growth is retarded and blood pressure is elevated. Hypertension may lead to heart failure.

Increased susceptibility to infection may produce septicemia. These children are easily fatigued with weakness and personality changes.

In older children, gradual onset of obesity, short stature, deceleration or cessation of growth may be the only early manifestation purplish striae on hips, abdomen and thigh are common. Older children most often have more severe obesity of the face and trunk. Buffalo hump and generalized obesity, signs of abnormal masculinization is seen. There may be hypertrichosis trunk compared with the extremities. Deepening of the voice, acne, enlargement of clitoris are seen in girls. Pubertal development may be delayed. Amenorrhea may occur in girls. Weakness, headache, and emotional lability may be prominent. Hypertension and hyperglycemia usually occur; hyperglycemia may progress to frank diabetes. Osteoporosis common and may cause pathologic fractures.

The earliest, most reliable indicators of hypercortisolism in children are weight gain and growth arrest. The obesity of pediatric Cushing disease is initially generalized rather than centripetal. Psychological disturbances, including compulsive overachieving behavior and emotional lability are distinct from the depression typically seen in adults. There can be a substantial degree of bone loss and undermineralization. Cushing syndrome caused by adrenal carcinoma or ectopic ACTH syndrome can follow a rapid fulminant course.

#### GENERAL FEATURES

- Rounded face
- Growth is retarded
- Fatigue

## DIAGNOSIS

### Blood

- *Plasma cortisol concentrations:* These are elevated, with loss of the normal diurnal variation in cortisol secretion. Determination of cortisol level between midnight and 2 AM may be a sensitive indicator of loss of variation.
- *Serum chloride and potassium concentrations:* These values may be lowered. Serum sodium and bicarbonate concentrations may be elevated (metabolic alkalosis).
- *Serum ACTH concentrations:* ACTH concentrations are slightly elevated with adrenal hyperplasia (Cushing disease), decreased in cases of adrenal tumor and greatly increased with ACTH producing pituitary or extrapituitary tumors.



- *The leukocyte count:* This measurement shows polymorphonuclear leukocytosis with lymphopenia and eosinophil count is low. The erythrocyte count may be elevated.

## Urine

- *Urinary free cortisol excretion:* This value is elevated. This is currently considered the most useful initial diagnostic test.
- *Urinary 17-hydroxycorticosteroid excretion (excretion products of the glucocorticoids):* This value is elevated.
- *Urinary 17-ketosteroid excretion:* This is usually elevated in association with adrenal tumors.
- *Glycosuria:* This finding may be present.

## Response to Dexamethasone Suppression Testing

There is diminished suppression of adrenal function after a small dose (0.5 mg) of dexamethasone. In *low dose dexamethasone test* 0.5 mg of dexamethasone is given every 6 hours for 2 days. The levels of urinary 17-OHS will fall below 1.5 mg/m<sup>2</sup>/24 h. Serum ACTH levels may be increased. The larger doses of dexamethasone cause suppression of adrenal activity when the disease is due to adrenal hyperplasia. Adenomas and adrenal carcinomas may rarely be suppressed by large doses of dexamethasone (4–16 mg/day in four divided doses).

Cortisol levels in blood are normally highest at 8 AM and decreases to less than 50% by midnight except in infants and young children in whom a diurnal rhythm is not always established. In patients with Cushing syndrome this circadian rhythm is lost; midnight cortisol levels >4.4 µg/dL strongly suggest the diagnosis. It is difficult to obtain diurnal blood samples as a part of an outpatient evaluation, but cortisol can be measured in saliva samples, which can be obtained at home at the appropriate times of day. Elevated night-time salivary cortisol levels raise suspicion for Cushing syndrome.

A glucose tolerance test is often abnormal but is of no diagnostic utility. Levels of serum electrolytes are usually normal, but potassium may be decreased, especially in patients with tumors that secrete ACTH ectopically.

Next step is to decide whether Cushing syndrome is ACTH-dependent or independent by estimation of plasma ACTH.

If circulating ACTH is suppressed to less than 10 pg/mL, it suggests ACTH-independent Cushing syndrome, most likely clue to adrenal cause.

## Radiograph

It is to determine the anatomical site of lesion by radiological investigations.

Once ACTH-independent Cushing syndrome is confirmed, adrenal computed tomography (CT) or magnetic resonance imaging (MRI) should be performed to detect the type of adrenal lesion—unilateral or bilateral, or benign adenoma or carcinoma.

Pituitary imaging may demonstrate a pituitary adenoma. This can be used in conjunction with pituitary venous sampling for localization of ACTH secreting adenomas. Adrenal imaging (e.g., CT scan) may demonstrate adenoma or bilateral hyperplasia.

Radionuclide studies of the adrenals may be useful in complex cases. Sellar tomography is indicated though the pituitary cell is usually normal. The thymic shadow is absent because excessive cortisol produces the involution.

Osteoporosis (evident first in the spine and pelvis) with compression fractures may occur in advanced cases, and skeletal maturation is usually delayed. Osseous maturation is usually moderately retarded but may be normal. Osteoporosis is common. Pathological fractures are noted.

CT detects virtually all adrenal tumors larger than 1.5 cm in diameter. MRI may detect ACTH-secreting pituitary adenomas, but many are too small to be seen; the addition of gadolinium contrast increases the sensitivity of detection. Bilateral inferior petrosal blood sampling to measure concentrations of ACTH before and after corticotropin-releasing hormone administration may be required to localize the tumor when a pituitary adenoma is not visualized; this is not routinely available in many centers, and moreover may be of decreased specifically children.

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes obesity, precocious puberty and Frohlich syndrome.

## TREATMENT

In all cases of primary adrenal hyperfunction due to tumor, surgical removal is indicated. ACTH should be given preoperatively and postoperatively to stimulate the nontumorous contralateral adrenal cortex, which is generally atrophied.

Glucocorticoids should be administered parenterally in pharmacologic doses during and after surgery until the patient is stable. Supplemental oral glucocorticoids, potassium, salt and

mineralocorticoids may be necessary until the suppressed contralateral adrenal gland had recovered, sometimes over a period of several months.

If a pituitary adenoma does not respond to treatment or if ACTH is secreted by an ectopic metastatic tumor, the adrenal glands may need to be removed. This can often be accomplished laparoscopically. Adrenalectomy may lead to increased ACTH secretion by an unresected pituitary adenoma, evidenced mainly by marked hyperpigmentation; this condition is termed Nelson syndrome.

If the lesion is benign cortical adenoma unilateral, adrenalectomy is indicated. If adenoma is bilateral, then the treatment of choice is subtotal adrenalectomy. Trans-sphenoidal pituitary microsurgery is the treatment of choice in Cushing disease.

Management of patients undergoing adrenalectomy requires adequate preoperative and postoperative replacement therapy with a corticosteroid. Tumors that produce corticosteroids usually lead to atrophy of the normal adrenal tissue, and replacement with cortisol (10 mg/m<sup>2</sup>/24 h in three divided doses after the immediate postoperative period) is required until there is recovery of the hypothalamic pituitary-adrenal axis. Postoperative complications may include sepsis, pancreatitis, thrombosis, poor wound healing, and sudden collapse, particularly in infants with Cushing syndrome. Substantial catch-up growth, pubertal progress, and increased bone density

occur, but bone density remains abnormal and adult height is often compromised.

Trans-sphenoidal pituitary microsurgery is the treatment of choice in pituitary Cushing disease in children. The overall success rate with follow-up of less than 10 years is 60–80%. Low postoperative serum or urinary cortisol concentrations predict long-term remission in the majority of cases. Relapses are treated with reoperation or pituitary irradiation.

Pasireotide, a somatostatin analog, can inhibit ACTH secretion, and is approved for use in adults with persistent disease after surgery or in whom surgery is contraindicated.

Irradiation of the pituitary gland may be considered. Cyproheptadine blocks the ACTH release and can be tried with Cushing disease. Patients with metastasis are treated with mitotane (o, p-DDD) or cisplatin.

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# Diabetes Insipidus

## PRESENTING COMPLAINTS

A 3-year-old girl was brought with the complaints of:

- Frequency of micturition since 6 months
- Passing large amount of urine since 6 months
- Bed wetting since 6 months

## History of Presenting Complaints

A 3-year-old girl was brought by the mother with history of passing large quantities of urine since 6 months. Mother told that her daughter will go to pass urine more frequently and she passes large quantities of urine every time. There was no history of burning sensation while passing the urine. Mother also revealed that her daughter drinks lots of water and she even passes urine in the night time.

## Past History of the Patient

She was the only sibling of the nonconsanguineous marriage. She was born at full term by normal delivery. Her birth weight was 3 kg. She started taking breast milk immediately after the delivery.

There was no significant postnatal event. Weaning was started in the 4th month and completed by 1 year. She was immunized completely and all the developmental milestones were normal.

## EXAMINATION

The girl was moderately built and nourished. She was sitting comfortably and was very co-operative. Anthropometric measurements included height 90 cm (50th centile), weight was 12 kg (50th centile). There were signs of mild dehydration.

The child was afebrile. The pulse rate was 120 per minute. The respiratory rate was 20 per minute. The blood pressure recorded was 70/50 mm Hg. There was no pallor, no lymphadenopathy, no cyanosis and no clubbing.

All the system examination were normal.

## INVESTIGATION

Hemoglobin	: 11 g/dL
TLC	: 9,000 cells/cu mm
DLC	: $P_{68} L_{28} E_2 M_2$
ESR	: 20 mm in the 1st hour
Urine specific gravity	: 1001
Osmolality	: 100 mOsm/kg water
Urine routine	: Albumin—nil Sugar—nil Microscopy—normal
Skull X-ray	: NAD
Chest X-ray	: NAD

## DISCUSSION

Diabetes insipidus results from lack of antidiuretic hormone (ADH) or arginine vasopressin (AVP), from neurohypophysis. The deficiency may be partial, complete or transient.

Diabetes insipidus (DI) manifests clinically with polyuria and polydipsia and can result from either vasopressin deficiency (central DI) or vasopressin insensitivity at the level of the kidney (nephrogenic DI). Both central DI and nephrogenic DI can arise from inherited defects of

### CASE AT A GLANCE

#### Basic Findings

Height	: 90 cm (50th centile)
Weight	: 12 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 120 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Passing large amount of urine
- Drinks lots of water
- Nocturia

##### Examination

- NAD

##### Investigation

- Urine specific gravity: 100
- Urine osmolality: 100 mOsm/kg water
- Urine routine: NAD

congenital or neonatal onset or can be secondary to a variety of causes.

Vasopressin, secreted from the posterior pituitary, is the principal regulator of tonicity, its release is largely stimulated by increased plasma tonicity. Vasopressin exerts its principal effect on the kidney via  $V_2$  receptors located primarily in the collecting tubule, the thick ascending limb of the loop of Henle, and the periglomerular tubules.

Activation of the  $V_2$  receptor results in increase in intracellular cyclic adenosine monophosphate, which leads to the insertion of the aquaporin-2 water channel into the apical (luminal) membrane. This allows water movement along its osmotic gradient into the hypertonic inner medullary interstitium from the tubule lumen and excretion of concentrated urine.

## CENTRAL DIABETES INSIPIDUS

### Causes of Central Diabetes Insipidus

#### *Congenital:*

- Optic nerve hypoplasia (septo-optic dysplasia)
- Ectopic or absent pituitary
- Other midline craniofacial defects

#### *Familial:*

- Autosomal dominant
- Autosomal recessive
- Wolfram syndrome [DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness)]-autosomal recessive

#### *Acquired:* Postoperative (with triple-phase response)

#### *Neoplasms:*

- Craniopharyngioma
- Germinoma
- Pinealoma
- Optic glioma

#### *Metastatic tumors:*

- Leukemias
- Infiltrative/autoimmune
- Sarcoidosis

#### *Trauma:* Transection of the stalk

#### *Drugs:*

- Ethanol
- Phenytoin
- Opiate antagonists

#### *Septic shock (infarction):*

- Sheehan syndrome (postpartum hemorrhage)
- Hypoxic brain injury

#### *Infections:*

- Basal meningitis
- Encephalitis
- Aneurysm and cysts

Central diabetes insipidus, a result of vasopressin deficiency, is caused by defects in hypothalamic vasopressin syntheses, packaging or transport along the neurohypophyseal tract to the posterior pituitary gland.

Genetic causes of vasopressin deficiency are rare and include inherited mutations in the vasopressin structural gene, defects in the neurophysin protein, and the MOAD syndrome (diabetes mellitus, diabetes insipidus, optic atrophy and deafness).

Autosomal dominant central DI usually occurs within first 5 years of life and results from mutations in the vasopressin gene. Central DI can result from multiple etiologies, including genetic mutations in the vasopressin gene; trauma (accidental or surgical) to vasopressin neurons; congenital malformations of the hypothalamus or pituitary; neoplasms; infiltrative, autoimmune, and infectious diseases affecting vasopressin neurons or fiber tracts; and increased metabolism of the vasopressin. In approximately 10% of children with central DI, the etiology is idiopathic.

Midline brain abnormalities such as septo-optic dysplasia and holoprosencephaly may also be associated with central diabetes insipidus. Accidental or surgical trauma to the axons of the vasopressin containing neurons can lead to transient or permanent diabetes insipidus. The triphasic response following surgery refers to an initial phase of transient DI, lasting for 12–48 hours, followed by a 2nd phase of syndrome of inappropriate antidiuretic hormone secretion, lasting up to 10 days, which may be followed by permanent DI. The initial phase may be the result of local edema interfering with normal vasopressin secretion; the 2nd phase results from unregulated vasopressin release from dying neurons, whereas in the 3rd phase, permanent DI results if more than 90% of the neurons have been destroyed.

Hypothalamic tumors and infiltrative diseases occur in significant number of children who present with diabetes insipidus. In patients with craniopharyngiomas, diabetes insipidus usually develops only after surgical intervention. This is in contrast to germinomas in which diabetes insipidus is often the presenting symptom.

Germinomas may be undetectable by magnetic resonance imaging (MRI) for several years; consequently, children with unexplained diabetes insipidus should have regularly repeated MRI scans. Infiltrative diseases such as histiocytosis and lymphocytic hypophysitis are other causes of diabetes insipidus in children. In these conditions,

as well as germinomas, MRI scan characteristically show thickening or a mass within the infundibular stalk.

## NEPHROGENIC DIABETES INSIPIDUS

Nephrogenic diabetes insipidus (NDI) is a disorder in which the collecting tubule is unresponsive to vasopressin.

Urine osmolality ranges from 50 to 1200 mOsm/kg in adults and from 50 to 500 mOsm/kg in neonates. The urine osmolality is dependent on the formation of a hypertonic medullary interstitium and the secretion of vasopressin. Vasopressin binds to the vasopressin 2 receptor and acts on the collecting tubule to increase passive water transport through the insertion of water channels (designated aquaporin-2) by exocytotic insertion into the luminal membrane, which increases collecting tubule water permeability. The hypertonic medullary interstitium is formed by the countercurrent system.

### Causes of Nephrogenic Diabetes Insipidus

#### *Congenital:*

- X-linked  $V_2$  receptor defect
- *Autosomal dominant:* Aquaporin-2 defect
- *Autosomal recessive:* Aquaporin-2 defect

#### *Acquired:*

- Metabolic
- Hypercalcemia
- Hypercalciuria
- Hypokalemia

#### *Renal diseases:*

- Polycystic kidney disease
- Medullary cystic kidney
- Sick cell nephropathy (disease/trait)
- Chronic pyelonephritis
- Acute tubular necrosis
- Obstructive uropathy

#### *Drugs:*

- Lithium
- Demeclocycline
- Amphotericin B
- Foscarnet
- Rifampin

Nephrogenic diabetes insipidus is attributed to inability of the kidney to respond to ADH. A psychogenic form of polydipsia with associated polyuria is attributed to compulsive water drinking. Diabetes insipidus with diabetes mellitus, optic atrophy and deafness is known as Wolfram syndrome or MOAD syndrome.

Nephrogenic (vasopressin-insensitive) DI (NDI) can result from genetic or acquired causes. Genetic causes are less common but more severe than acquired forms of NDI. The polyuria and polydipsia associated with genetic NDI usually occur within the first several weeks of life, but may only become apparent after weaning or with longer periods of night-time sleep. Many infants initially present with fever, vomiting, and dehydration. Failure to thrive may be secondary to the ingestion of large amounts of water, resulting in caloric malnutrition. Longstanding ingestion and excretion of large volumes of water can lead to nonobstructive hydronephrosis, hydroureter, and megabladder.

Congenital X-linked NDI results from inactivating mutations of the vasopressin  $V_2$  receptor. Congenital autosomal recessive NDI results from defect in the *aquaporin-2* gene. An autosomal dominant form of NDI is associated with processing mutations of the *aquaporin-2* gene.

Acquired NDI can result from hyperkalemia or hypokalemia. Impaired renal concentrating ability can also be seen with ureteral obstruction, chronic renal failure, polycystic kidney disease, medullary cystic disease, Sjögren syndrome, and sickle cell disease.

### CLINICAL FEATURES (FIG. 1)

The onset of diabetes insipidus is often abrupt with polyuria and intense thirst. The affected child typically has nocturia or enuresis and cannot go through the night without drinking water. Cold water is typically the preferred fluid. Dehydration may occur if fluid intake is not sufficient to keep up

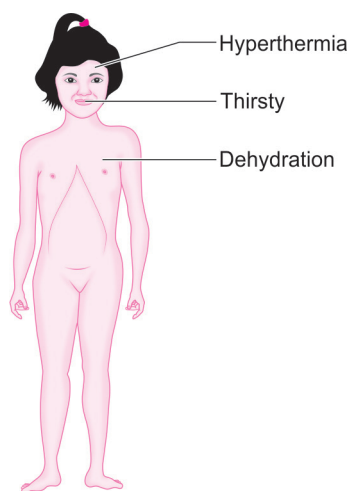


Fig. 1: Clinical features.



with urine losses or if there is concomitant damage to the normal thirst mechanism.

In infants, symptoms may also include failure to thrive, vomiting, constipation and unexplained fevers. It is especially difficult to recognize polyuria and polydipsia in a young infant on an ordinary feeding regimen and the infant may present with severe dehydration, circulatory collapse and convulsions. Familial diabetes insipidus may have a more insidious onset and a slowly progressive course.

Nephrogenic diabetes insipidus can present in the 1st week of life with irritability, vomiting, and unexplained fever. The infant will have repeated episodes of hypernatremic dehydration, which may be accompanied by seizures, until the diagnosis is made and therapy is initiated. Many infants with NDI initially present with fever, vomiting, and dehydration, often leading to an evaluation for infection. They may also have growth failure and mental retardation. Intracerebral calcification of the frontal lobes and basal ganglia is common in children with X-linked NDI.

Repeated episodes of hypernatremia can result in intellectual impairment. Patients often fail to thrive due to their need to ingest water at the expense of food. The enormous urine volumes can result in urinary tract dilatation.

#### GENERAL FEATURES

- Growth retardation
- Passing large quantities of water
- Nocturnal enuresis
- Poor appetite

#### ESSENTIAL DIAGNOSTIC POINTS

- Polydipsia and polyuria
- Urine specific gravity  $<1.010$
- Inability to concentrate urine after fluid restriction
- Hyperosmolality of plasma
- Subnormal plasma AVP concentration
- Responsiveness to AVP administration

### DIAGNOSIS

Initial investigations should include testing for urine sugar and early morning specific gravity or osmolality. Blood gas, urea, electrolytes, calcium and creatinine should be estimated. High plasma osmolality ( $>300$  mOsm/kg or serum sodium  $>146$  mmol/L) and low urine osmolality ( $<300$  mOsm/kg and urine specific gravity  $<1.005$ ) suggest the diagnosis of DI, which needs further classification on the basis of response to arginine vasopressin. Patients with normal plasma osmolality

and low urine osmolality ( $<800$  mOsm/kg) should undergo water deprivation test. Urinary osmolality  $>800$  mOsm/kg (specific gravity  $>1.010$ ) excludes DI.

Often the distinction between central and nephrogenic DI tilters a water deprivation test or desmopressin (DDAVP) test. During water deprivation test for minimum (3–6 hours, children with central and nephrogenic DI fail to concentrate urine and plasma more than 300 mOsm/kg, whereas there is urinary concentration in children with compulsory water drinking. If there is concentration of urine following DDAVP (5 µg intranasal), the cause is primary AVP deficiency.

Failure to concentrate urine and absence of response to DDAVP indicates nephrogenic DI.

### Water Deprivation Test

The test is indicated in children with polyuria, low urinary osmolality and normal plasma osmolality. The aim is to increase plasma osmolality above 300 mOsm/kg to allow opportunity for maximal renal concentration. Renal failure and renal tubular acidosis (RTA) should be excluded before the test. Water deprivation test is not required in the presence of hypernatremia. The test should be done on an inpatient basis due to risk of dehydration. Water deprivation is started early in the morning. The child should be weighed and target weight loss calculated (5% of total body weight). Body weight, urine output and urine and blood osmolality should be monitored hourly. The test should be stopped when urine osmolality increases above 800 mOsm/kg or specific gravity is more than 1.010.

Since this excludes DI, plasma osmolality increases above 300 mOsm/kg or serum sodium is above 146 mEq/L (target achieved) or weight loss is more than 5% (risk of dehydration). Urine osmolality below 300 mOsm/kg in the presence of plasma osmolality above 300 mOsm/kg confirms DI. These patients should be evaluated further with response to vasopressin. Children with urine osmolality between 300 and 800 mOsm/kg with plasma osmolality above 300 mOsm/kg may have partial central or nephrogenic DI.

The child should be observed carefully during water deprivation test to ensure compliance and to prevent severe dehydration. Administration of desmopressin, DDAVP (10 µg intranasal) raises the urine osmolality. Failure to concentrate urine and absence of response to DDAVP indicate nephrogenic diabetes insipidus. Definitive tests of renal function are indicated in them.

## Vasopressin Response Test

This test is performed for differentiation of complete central DI from nephrogenic DI. Urine osmolality is measured 1 and 4 hours after vasopressin injection (0.1 unit/kg). An increase in urine osmolality by more than 50% of baseline levels is diagnostic of central DI while a smaller increase suggests nephrogenic DI.

Once the diagnosis of CDI has been established as explained earlier MRI should be obtained. MRI is not very helpful in distinguishing CDI from NDI, but will help establish the underlying cause of CDI. The posterior pituitary “bright spot” is diminished or absent in both forms of DI, normal in primary polydipsia, and decreased in syndrome of inappropriate antidiuretic hormone secretion (SIADH). In patients with CDI who have normal brain MRI on diagnosis, serial imaging over time should be obtained as the cause may be evident years later. Quantitative measurement of the beta subunit of human chorionic gonadotropin, often secreted by germinomas and pinealomas, should be performed in children with idiopathic or unexplained CDI.

For the postsurgical patient, it is important to differentiate the normal increased diuresis from CDI. Serum osmolality will be high in acute postsurgical CDI, whereas it will be low or normal in cases of polyuria due to the normal diuresis of intraoperative fluids. The intraoperative fluid record should also help distinguish between these two possibilities. In patients with coexisting vasopressin and cortisol deficits, symptoms of DI may be masked because cortisol deficiency impairs renal free water clearance. In such cases, glucocorticoid therapy may precipitate polyuria, leading to the diagnosis of DI.

## Radiologic Studies

MRI may reveal evidence for intracranial tumor such as calcification, enlargement of sella, erosion of clinoid process and increased width of suture lines or evidence of reticuloendotheliosis such as rarefaction. MRI also can demonstrate the absence of the bright hyperintense spot in hypothalamic-pituitary lesions.

X-ray of skull may reveal evidence for intracranial tumor such as calcification, enlargement of sella, erosion of clinoid process and increased width of suture lines or evidence of reticuloendotheliosis such as rarefaction. CT or MRI scans are indicated for evaluation of posterior pituitary.

### LABORATORY SALIENT FINDINGS

- Hypotonic urine and hypertonic serum
- Urine specific gravity: <1.010; osmolality <300 mOsm/kg
- Serum AVP concentration
- MRI scan to evaluate for tumors or infiltrative process
- CT scan
- X-ray of the skull

## TREATMENT OF CENTRAL DIABETES INSIPIDUS

### Fluid Therapy

Neonates and young infants are often best treated solely with fluid therapy, given their requirement for large volumes (3 L/m<sup>2</sup>/24 h) of nutritive fluid. The use of vasopressin analogs in patients with obligate high fluid intake is difficult given the risk of life-threatening hyponatremia. The use of diluted parenteral and lyophilized long-acting vasopressin analog DDAVP (desmopressin) has been successfully administered to infants with central DI both subcutaneously and orally without causing severe hyponatremia.

### Vasopressin Analogs

Treatment of central DI in older children is best accomplished with the use of DDAVP. DDAVP is available (onset 15–30 minutes). The intranasal preparation of DDAVP (2.5–10 µg/0.1 mL every 12 hourly) can be administered by rhinal tube (allowing dose titration) or by nasal spray. Use of DDAVP oral tablets requires at least a 10-fold increase in the dosage compared with the intranasal preparation. Oral dosages of 25–300 µg every 8–12 hours are safe and effective in children. The appropriate dosage and route of administration is determined empirically based on the desired length of antidiuresis and patient preference.

### Aqueous Vasopressin

Central DI of acute onset following neurosurgery is best managed with continuous administration of synthetic aqueous vasopressin. Under most circumstances, total fluid intake must be limited to 1 L/m<sup>2</sup>/24 h during antidiuresis. A typical dosage for intravenous vasopressin therapy is 1.5 mL/kg/h, which results in a blood vasopressin concentration of approximately 10 µg/mL. Vasopressin concentrations >1,000 µg/mL should be avoided because they can cause cutaneous necrosis, rhabdomyolysis, cardiac rhythm disturbances, and hypertension: Postneurosurgical patients treated

with vasopressin infusion should be switched from intravenous to oral fluids as soon as possible to allow thirst sensation, if intact, to help regulate osmolality.

*Neurogenic diabetes insipidus* is treated by administration of desmopressin (DDAVP), an analog of ADH given as a nasal spray. The usual dose is 5–10 µg daily either as a single dose or divided into two doses. Children under 2 years require lesser doses (0.15–0.50 µg/kg). An oral preparation of DDAVP (0.2 mg) is also available now.

Oral administration of chlorpropamide 20 mg/kg/24 h in two divided doses may reduce polyuria and polydipsia in partial deficiency. Hypoglycemia is a major side effect. Chlorpropamide potentiates the residual secretion of ADH and also has effect on the thirst center.

## TREATMENT OF NEPHROGENIC INSIPIDUS

The treatment of acquired NDI focuses on eliminating, if possible, the underlying disorder, such as offending drugs, hypercalcemia, hypokalemia, or ureteral obstruction. Congenital nephrogenic DI is often difficult to treat. The main goals are to ensure the intake of adequate calories for growth and to avoid severe dehydration. Even with the early institution of therapy, however, growth failure and developmental disabilities are common.

*Nephrogenic diabetes insipidus*: Solute load should be decreased and sufficient water should be given to prevent dehydration. Hydrochlorothiazide 0.5–1.5 mg/kg/day reduces urinary volume as

a paradoxical effect. Addition of indomethacin 1–2 mg/kg/24 h is beneficial in some. Chlorpropamide is not useful in nephrogenic diabetes insipidus.

Pharmacologic approaches to the treatment of NDI include the use of thiazide diuretics and are intended to decrease the overall urine output. Thiazides appear to induce a state of mild volume depletion by enhancing sodium excretion at the expense of water and by causing a decrease in the glomerular filtration rate, which results in proximal tubular sodium and water reabsorption. Indomethacin and amiloride may be used in combination with thiazides to further reduce polyuria, high dose DDAVP therapy, in combination with indomethacin, has been used in some subjects with NDI. This treatment could prove useful in patients with genetic defects in the  $V_2$  receptor associated with a reduced binding affinity for vasopressin.

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# Diabetes Mellitus

## PRESENTING COMPLAINTS

A 6-year-old boy was brought with the complaints of:

- Loss of weight since 6 months
- Tiredness since 6 months
- Increased frequency of urine since 6 months

## History of Presenting Complaints

A 6-year-old boy was brought to the pediatric outpatient department with the history of drastic loss of weight since last 6 months. His mother was very much worried about the loss of weight. Mother gave the history that his son was weighing about 22 kg 6 months back, now he has reduced to 18 kg. She revealed that she had noticed that her son was more frequently passing the urine. There was no burning sensation. She also told that her son gets up in the night to pass urine.

Mother informed that her son's eating habits were normal. Of late she noticed tiredness in her son for which she showed him to the family doctor who advised some B-complex syrup. She also pointed out the school absenteeism from the last 3 months.

## Past History of the Patient

He was the elder sibling of nonconsanguineous marriage. He was born at full term by normal delivery. He cried immediately after the delivery. His birth weight was 3 kg. He was exclusively on breast milk for the first 3 months. Later weaning was started and he was on family food by 15 months. His developmental milestones were normal. He was immunized completely. School absenteeism was present since last 3 months.

## EXAMINATION

The boy was moderately built and nourished. He was conscious and looking tired. Anthropometric measurements included the height 124 cm (95th centile), the weight was 15 kg (50th centile).

Child was afebrile. The pulse rate was 86 per minute. Respiratory rate was 20 per minute. Blood pressure recorded was 90/70 mm Hg. There was pallor. Presence of folded skin indicating recent weight loss were present. All the systemic examination were normal.

## INVESTIGATION

Hemoglobin	: 9 g/dL
TLC	: 8,700 cells/cu mm
DC	: $P_{72} L_{18} E_6 M_2 B_2$
ESR	: 26 mm in the 1st hour
RBS	: 300 mg/dL
FBS	: 130 mg/dL
Urine	: Albumin ++ Sugar +++ Ketone bodies + 1-2 RBCs/HPF 6-7 pus cells/HPF

### CASE AT A GLANCE

#### Basic Findings

Height	: 124 cm (95th centile)
Weight	: 15 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 86 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 90/70 mm Hg

#### Positive Findings

##### History

- Loss of weight
- Polyuria
- School absenteeism

##### Examination

- Poor nourished
- Evidence of recent loss of weight
- Pallor

##### Investigation

- Hb: 9 g/dL
- RBS: 300 mg/dL
- FBS: 130 mg/dL
- Urine: Sugar ++  
Ketone bodies +++

DISCUSSION

History of weight loss since last 6 months along with normal food intake. There was history of nocturia. This along with the laboratory findings of presence of sugar and ketone bodies and raised blood glucose level clinches the diagnosis of diabetes mellitus.

Diabetes mellitus is a chronic disease caused by deficiency of insulin, which is secreted by the beta cells of pancreas. The illness is characterized by hyperglycemia and glucosuria. Diabetes may also result from defects of insulin action. The disease causes long-term damage, dysfunction or failure of various organs including the eyes, kidneys, nerves, heart and blood vessels.

CLASSIFICATION

Diabetes is usually classified as type 1 and type 2. Type 1 diabetes is usually a disease of young people and thus much more frequent in children. Children with type 1 diabetes have to rely on lifelong insulin therapy. Thus, this type was also known as insulin-dependent diabetes mellitus (IDDM). Type 2 was previously known as noninsulin-dependent diabetes mellitus (NIDDM). Other distinguishing features of types 1 and 2 diabetes are given in **Table 1**.

Type 1A diabetes occurs from immunologic damage to the insulin-producing  $\beta$ -cells of the pancreatic islets. The damage occurs gradually-over months or years in most people and symptoms do not appear until about 90% of the pancreatic islets have been destroyed. The immunologic

damages has a genetic predisposition and is probably affected by environmental factors.

There is an association with HLA-DR3 and HLA-DR4, and about 95% of white diabetic children have at least one of these HAL types. The presence of aspartic acid on position 57 of the—DQ beta chain of the HLA complex is associated with protection from type 1 diabetes.

Antibodies to islet cells (ICA), insulin, “64 K” or glutamic acid decarboxylase (GAD), ICA512 (IA-2), and other antibodies are present in the serum of over 90% of patients who will develop type 1A diabetes for months to years prior to diagnosis. These antibodies are probably the effect and not the cause of islet  $\beta$ -cell destruction.

The etiology of type 2 diabetes has been related to a number of genetic alterations. All have the common denominator of a reduced sensitivity to insulin.

PATHOGENESIS

Pathogenesis is multifactorial. Genetic alterations located on chromosome 6 may initiate  $\beta$ -cell damage. Autoimmune destruction of  $\beta$  cells has been demonstrated in children with type 1 DM.

Environmental factors trigger the onset of autoimmunity in genetically susceptible individuals. Infections (mumps, coxsackievirus B3 and B4 and cytomegalovirus), toxins (rodenticides and nitrosamines) and early introduction of cow’s milk protein may be important factors in the subsequent development of diabetes in genetically susceptible individuals.

CLINICAL FEATURES (FIG. 1)

Clinical features manifest only when more than 90% of the pancreatic  $\beta$ -cell synthesis and release capacity has been destroyed or effectively inactivated.

TABLE 1: Distinguishing features of type 1 and 2 diabetes.		
Features	Type 1	Type 2
Onset	Rapid, obvious	Slow, insidious
Age of onset	Before 30 years	After 30 years
Obesity	No role	Predisposing
Association with HLA DR3 and 4	2.5 times	Equal to normal
Family history	10%	Strong
Concordance in identical twins	25–50%	Nearly 100%
Anti-islet cell antibody	>80%	<5%
Ketoacidosis	Frequent	Absent
Microvascular complications	Rare at onset	May be present
Need for insulin	Universal	Uncommon

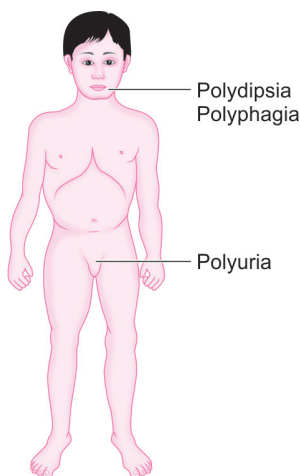
GENERAL FEATURES
<ul style="list-style-type: none"><li>• Fatigue</li><li>• Loss of weight</li><li>• Failure to thrive</li></ul>

Initial symptoms include polyuria, polydipsia, polyphagia and fatigue. Diabetic ketoacidosis (DKA) supervenes in more than half of the children.

The final stage is total diabetes, which refers to complete  $\beta$ -cell destruction with no capacity of endogenous insulin synthesis or release. This is irreversible.

Total diabetes is considered to have reached when the insulin requirement of a preadolescent





**Fig. 1:** Clinical features.

has plateaued at approximately 0.8 units/kg/day and in an adolescent at about 1.0 unit/kg/day.

Suspect diabetes mellitus in a child with the classical triad of polyuria, polydipsia and polyphagia. Random plasma glucose concentration >200 mg/dL on two separate occasions with symptoms of diabetes suggest the diagnosis. Fasting plasma glucose levels >126 mg/dL on two occasions is also suggestive of the diagnosis of diabetes.

In patient who presents with the classical symptoms of polyuria, thirst and weight loss, the diagnosis of diabetes is straightforward, and requires only the demonstration of hyperglycemia. To a child with an accidental finding of glycosuria, one must differentiate diabetes mellitus from renal glycosuria or Fanconi syndrome. Ketonuria can occur in starvation, and in adolescents, after an alcohol binge on an empty stomach. Both these conditions will not be accompanied by hyperglycemia and ketonemia will be mild (not positive in dilute serum).

The child presenting with acidosis must be differentiated from other causes of metabolic acidosis with increased anion gap, like uremia, lactic acidosis and salicylate poisoning. Every child presenting in a coma must have a blood sugar and urine ketone to detect DKA.

## DIFFERENTIAL DIAGNOSIS OF POLYURIA

### Diabetes Mellitus

Diabetes mellitus presents with polydipsia, polyphagia, recurrent infections and weight loss in addition to polyuria.

## Renal Disorders

Polyuria is common in obstructive uropathy. It is often the presenting feature of tubular disorders like renal tubular acidosis, Bartter syndrome and Gitelman syndrome. These conditions are associated with severe failure to thrive and rickets.

## Inefficient Aldosterone Action

These include adrenal insufficiency, isolated aldosterone deficiency or aldosterone resistance. They present with hyponatremia, hyperkalemia and dehydration. The condition may be lethal. Failure to thrive is common. Pigmentation is characteristic of adrenal insufficiency, polyuria and salt wasting in the neonatal period should prompt evaluation for congenital adrenal hyperplasia. Genital ambiguity in girls may be the only clue to this diagnosis.

Excessive water drinking (psychogenic polydipsia). The condition is extremely rare and is a diagnosis of exclusion.

### ESSENTIAL DIAGNOSTIC POINTS

- Polyuria, polydipsia, and weight loss
- Hyperglycemia and glucosuria with or without ketonuria

## COMPLICATIONS

Complications can be classified as acute, intermediate and chronic.

The acute complications include ketoacidosis and hypoglycemia. These are usually reversible.

Intermediate complications include lipodystrophy, growth failure, impaired intellectual development and hypoglycemia unawareness. These are potentially reversible.

Chronic complications are irreversible and are due to micro and macrovascular pathology. These include retinopathy, neuropathy and nephropathy. The following section shall discuss two most common acute complications, i.e., hypoglycemia and diabetic ketoacidosis.

## Hypoglycemia

Hypoglycemia is defined as blood glucose levels less than 60 mg/dL. It is characterized by adrenergic symptoms such as sweating, pallor, trembling and tachycardia. Untreated, this may progress to drowsiness, confusion, coma and seizures. The diagnosis should be confirmed by a quick blood test. Simple carbohydrates like sugar, glucose, honey, fruit juice or carbonated drinks may be offered immediately. An unconscious

child should be given intravenous 25% dextrose (2–4 mL/kg) or glucagons (0.5 mg in children, 1.0 mg in adolescents) intramuscularly.

#### LABORATORY SALIENT FINDINGS

- Random blood glucose level above >300 mg/dL
- Fasting blood glucose level above >200 mg/dL
- Ketonuria

## Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is the most common and severe manifestation of diabetes. It occurs as a result of insulin deficiency with concomitant increased production of the stress hormones, glucagons, cortisol and growth hormone. The prime responses include increased gluconeogenesis, glycogenolysis and ketone body production as well as decreased glycogen synthesis.

### Clinical Features

Precipitating factors for diabetic ketoacidosis include intercurrent illness, trauma and obscure infection. Manifestations include symptoms of hyperglycemia and ketoacidosis such as polyuria, nocturia, polydipsia, polyphagia, weight loss, lethargy, weakness, nausea, vomiting, change in level of consciousness, increased respiratory rate with Kussmaul breathing and abdominal pain. The child is acidotic and has deep rapid breathing with severe dehydration. Blood pressure, pulse rate, skin turgor and body weight should be taken to evaluate dehydration.

### Diagnosis

Criteria for confirmation of diagnosis of DKA include ketonuria, ketonemia, blood glucose >250 mg/dL, blood pH less than 7.3 and serum bicarbonate less than 20 mEq/L. Serum potassium levels may be high. Urinalysis may reveal the presence of glucose and acetoacetate/acetone.

#### ESSENTIAL DIAGNOSTIC POINTS OF DIABETIC KETOACIDOSIS

- Triad of metabolic derangement: hyperglycemia, ketonuria, and acidosis.
- Abdominal pain may mimic appendicitis.
- Hyperventilation can mimic pneumonia.
- Administer insulin promptly to prevent ketone and acid production.
- Total body potassium is usually significantly diminished.
- Cerebral edema is the most common cause of death.
- Avoid excess fluid therapy because of the risk of cerebral edema.

## Managing Ketoacidosis

The aim of management should be to restore normal hemodynamic status, normal acid-base balance and slowly correct blood glucose to a range that is not acutely dangerous.

The main strategies of therapy include (i) replacement of water and electrolytes and (ii) starting insulin. Replacement of fluid is essential for maintaining hemodynamic stability and to prevent lactic acidosis and poor perfusion.

### Fluid Therapy

- Immediately secure a venous access and obtain blood samples for counts, sugar, urea, sodium, potassium, etc., an arterial sample should be taken for blood gas and pH estimation.
- Start IV fluids. The initial fluid should be normal saline (0.9%) IV given in a dose of 20 mL/kg within the 1st hour of diagnosis.
- After 1 hour, continue with normal (0.45%) saline till signs of severe dehydration disappear. Infusion of maintenance fluids and deficit should be given over 24–36 hours.
- Monitor blood glucose levels hourly. Obtain simultaneous urine samples for documentation of glucosuria and ketonuria. When blood sugar falls to 300 mg/dL or less, 5% dextrose should be added to the infusate.
- Once the child has passed urine, add potassium (40 mEq/L of IV fluids). Potassium replacement is important because potassium shifts from extracellular to intracellular compartment during treatment.
- *Correction of acidosis:* Bicarbonate therapy is usually not necessary. Insulin therapy inhibits ketogenesis and stimulates the metabolism of ketone bodies. Bicarbonate is necessary if there is impending ventilatory and circulatory compromise.

### Insulin

- *Start insulin:* Give an initial bolus dose of 0.1 unit/kg IV followed by a continuous intravenous infusion at a rate of 0.1 unit/kg/h. In infants the dose may be reduced to 0.05 unit/kg/h. The aim is to decrease blood glucose by 50–100 mg/dL every hour.
- If there is no significant reduction in blood sugar, the dose can be increased to 0.2 units/kg/h.
- The usual practice is to add 1 unit/kg of insulin in 100 mL of 0.9% saline and administer at a rate of 10 mL/h (1 unit/kg/h).

- The intravenous tubing should be flushed with insulin prior to starting the infusion to avoid binding of insulin to plastic surfaces and reduced delivery of insulin.
- Reduce the dose rate to 0.5 units/kg/h when acidosis clears ( $\text{pH} > 7.3$ ) and blood glucose reaches 200 mg/dL. Urine ketones are not a good guide for monitoring insulin dose.
- The insulin infusion can be discontinued when the blood glucose levels fall into a normal range. However, it should be continued till 30 minutes after the administration of subcutaneous insulin.

### Monitoring

- Meticulously monitor the vital signs, state of consciousness, blood glucose and urine ketones till intravenous infusion is terminated.
- Monitor electrolyte and pH 2–4 hourly.
- Urine output should be checked every 4 hours.
- Watch for cerebral edema. This may occur due to rapid correction of hyperglycemia and hyperosmolality, excessive use of alkali, high doses of insulin and overhydration.

### Chronic Complications

In the past, about 30–40% of persons with type 1 diabetes eventually developed renal failure or loss of vision. Factors that greatly reduce this likelihood are longitudinal HbA levels in a good range, maintenance of blood pressure below the 90th percentile for age.

Annual retinal examinations and urine micro-albumin measurements are important for children aged 10 years or older who have diabetes for 3 years or longer. Data now show that the use of

angiotensin-converting enzyme inhibitors may reverse or delay kidney damage when it is detected in the microalbuminuria stage (20–300  $\mu\text{g}/\text{min}$ ). Similarly, laser treatment to coagulate proliferating capillaries prevents bleeding and leakage of blood into the vitreous fluid or behind the retina. This treatment helps to prevent retinal detachment and to preserve useful vision for many people with proliferative diabetic retinopathy.

The aim of immediate therapy is to restore fluid volume and return acid-base status to normal, and not to achieve stable euglycemia. When the patient is ready to take orally, with a blood pH of  $< 7.3$  and glucose less than 300 mg/dL, switch from intravenous to subcutaneous insulin. Start regular insulin (0.5 units/kg/day) in newly diagnosed children  $< 5$  years and 1.0 unit/kg/day in older children. Subsequently the child can be started on a split-mix regime.

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# Hypothyroidism

## PRESENTING COMPLAINTS

A 5-month-old girl was brought with the complaints of:

- Constipation since birth
- Delayed developmental milestones since 3 months

## History of Presenting Complaints

A 5-month-old girl was brought to the pediatric outpatient department with history of constipation and delayed developmental milestones. Mother gave the history that her child was passing motion once in 3 or 4 days since her birth. Now she was passing once in a week. Sometimes child may require laxatives. The child was passing stools sometimes like pellets. Child had not developed neck control. Social smile was not present. But she was responding to local noise or commands. Mother had noticed that her developmental

milestones were much delayed as compared to elder sibling.

## Past History of the Patient

She was second sibling of nonconsanguineous marriage. She was born at term and delivered by cesarean section. The indication of the section was nonprogression of the labor. The birth weight of the child was 3.5 kg. Child started taking breast milk immediately after birth. Child had prolonged physiological jaundice for which child had received phototherapy.

## EXAMINATION

On examination, the child was well built and nourished. She was lying on the examination table. She was not as active as the other children of her age. She was not moving on sideways. There was depressed nasal bridge. The mouth was kept open with protruding tongue. The hands were broad and fingers were short. Anthropometric measurements included, the length was 62 cm (80th centile), the weight was 7 kg (50th centile), the head circumference was 40 cm.

The child was afebrile. The heart rate was 110 per minute, the respiratory rate was 26 per minute. The blood pressure recorded was 60/50 mm Hg. There was no pallor, no edema, no icterus, and no lymphadenopathy. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 13 g/dL
TLC	: 7,600 cells/cu mm
DLC	: $P_{68}$ $L_{28}$ $M_2$ $B_2$
ESR	: 18 mm at 1st hour
T3 level	: 60 ng/dL (62–200 ng/dL)
T4 level	: 4 µg/dL (4.5–12.0 µg/dL)
TSH	: 0.10 IU/dL (0.30–5.5 IU/mL)
X-ray of the body	: Showed the delayed ossification of the acetabular roof

### CASE AT A GLANCE

#### Basic Findings

Length	: 62 cm (80th centile)
Weight	: 7 kg (50th centile)
Temperature	: 36°C
Pulse rate	: 110 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 60/50 mm Hg

#### Positive Findings

##### History

- Constipation
- Delayed motor development
- No social smile
- Prolonged physiological jaundice

##### Examination

- Depressed nasal bridge
- Open mouth
- Protruding tongue
- Broad hand

##### Investigation

- $T_3$  and  $T_4$ : Decreased
- TSH: Increased
- X-ray delayed: Delayed ossification of acetabular roofs

## DISCUSSION

Hypothyroidism is a common endocrinal disorder of the childhood. This can appear after a period of normal thyroid function. Then the disorder is named as acquired hypothyroidism. The cretinism is used to denote congenital hypothyroidism. Congenital hypothyroidism may be familial or sporadic, goitrous and nongoitrous.

Hypothyroidism results from deficient production of thyroid hormone, either from a defect in the gland itself (primary hypothyroidism) or a result of reduced thyroid-stimulating hormone (TSH) stimulation (central or hypopituitary hypothyroidism). The disorder may be manifested from birth (congenital) or acquired (juvenile hypothyroidism). When symptoms appear after a period of apparently normal thyroid function, the disorder may be truly acquired or might only appear so as a result of one of a variety of congenital defects in which the manifestation of the deficiency is delayed.

Most cases of congenital hypothyroidism are not hereditary and result from thyroid dysgenesis. Some cases are familial these are usually caused by one of the inborn errors of thyroid hormone synthesis (dyshormonogenesis) and may be associated with a goiter.

Although there are many causes of hypothyroidism in the newborn, most cases result from hypoplasia or aplasia of the thyroid gland, radioiodine therapy at the pregnancy, thyrotropin deficiency and defective synthesis of thyroxine. In 85% of cases, it is thyroid dysgenesis. In 10–15% cases it is inborn errors of thyroid hormone synthesis. They are inherited as autosomal recessive traits. Most infants with congenital hypothyroidism are detected by newborn screening programs in the first few weeks after birth, before obvious clinical symptoms and signs develop.

### CAUSES OF CONGENITAL HYPOTHYROIDISM

- *Primary:* Agenesis/dysgenesis, ectopic, dyshormonogenesis
- *Secondary:* Hypopituitarism, hypothalamic abnormality
- *Other:* Transient, maternal factors (e.g., goitrogen ingestion, iodide deficiency)

Of the genetically determined enzymatic defects that cause hypothyroidism, only Pendred syndrome (a defect in iodide organification with congenital nerve deafness) has distinguishing clinical features. In children who have enzymatic defects, thyroid enlargement is usually not present in the newborn period but occurs within the first

two decades of life. Although thyroid function tests (including radioactive iodide uptake studies) may be helpful in diagnosis, final clarification of the defect generally requires chromatographic fractionation of iodinated compounds in the serum, urine and thyroid tissue.

## CLINICAL FEATURES (FIG. 1)

Most infants with congenital hypothyroidism (Fig. 2) are asymptomatic at birth, even if there is complete agenesis of the thyroid gland. This situation is attributed to partial transplacental passage of maternal  $T_4$  which provides fetal levels that are approximately 33% of normal at birth. Despite this maternal contribution of hypothyroid infants still have a low serum  $T_4$  and elevated TSH level and so will be identified by newborn screening programs.

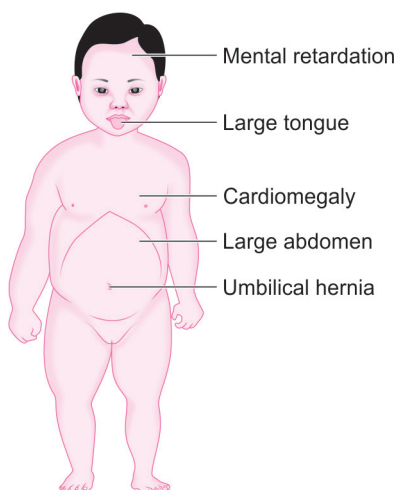


Fig. 1: Clinical features.

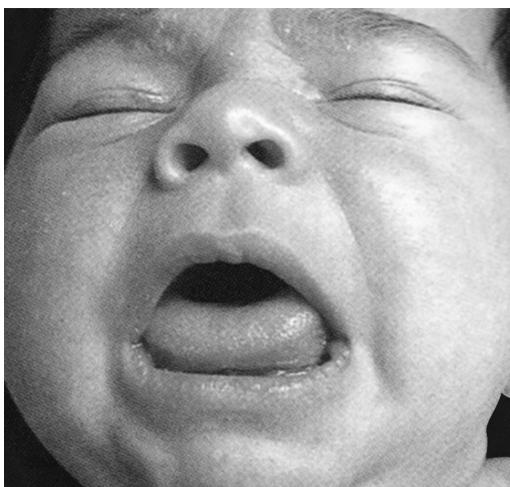


Fig. 2: Congenital hypothyroidism.



Clinical features may not be obvious for several weeks after birth. It is twice as common in girls as in boys. The infants may be significantly heavier at birth than the normal newborn infants. Most of the time, symptoms are subtle but can include lethargy, hoarse cry, feeding problems, constipation, macroglossia, umbilical hernia, large fontanels, hypotonia, dry skin, hypothermia, and prolonged jaundice. Some newborns with thyroid dysmorphogenesis can have a palpable goiter.

One of the earlier signs of congenital hypothyroidism is patent posterior fontanelle and wide-open cranial sutures. Head size may be slightly increased because of the myxedema of brain. There may be constipation which may not respond to laxative. This is attributed to in utero lag in skeletal maturation. Prolongation of physiologic jaundice, caused by delayed maturation of glucuronide conjugation, may be the earliest sign.

The severity of the findings in patients with thyroid deficiency depends on the age at onset and degree of deficiency. Congenital hypothyroidism is associated with an increased risk for congenital malformations when compared to the general population. The most commonly affected system is the heart, but the gastrointestinal tract, kidneys, urinary tract, and skeletal system are also affected.

Respiratory difficulties, partly caused by the large tongue, include apneic episodes, noisy respirations, and nasal obstruction. Some infants may develop respiratory distress syndrome. Affected infants cry little, sleep much, have poor appetites, and are generally sluggish. There may be constipation that does not usually respond to treatment.

Characteristic coarse facial features appear at the age of 8–10 weeks. These include puffy face, swollen eyelid, widely separated eyes, narrow palpebral fissure, broad nose with depressed bridge, open mouth with broad thick protuberant tongue. The neck is short and thick. Supraclavicular pad of fat may be present. The voice is hoarse. The muscles are flaccid and hypotonic.

They are lethargic and less active. Feeding difficulties occur due to presence of large tongue and include apneic episodes, noisy respiration and nasal obstruction. These infants cry little, sleep much and have poor appetite. There will be prolongation of physiological jaundice. This is because of delayed maturation of the glucuronide conjugation. These infants will have constipation, hypothermia is common.

The skin may be dry, thick, scaly and coarse with a yellowish tinge due to excessive deposition of carotene. The hair is dry, coarse and brittle

(variable) and may be excessive. Lateral thinning of the eyebrows may occur. The axillary and supraclavicular fat pads may be prominent in infants. Muscular hypertrophy (Kocher-Debre-Semelaig syndrome) is an unusual association with congenital hypothyroidism.

The abdomen is large, umbilical hernia may be present. The temperature is subnormal, often less than 35°C and the skin may be cold and mottled. Edema of the genitalia and extremities may be present. The pulse is slow, heart murmur and cardiomegaly and asymptomatic pericardial effusion are common.

Child's growth will be stunted, the extremities are short, and the head size is normal or even increased. The anterior fontanel is large and the posterior fontanel may remain open. The eyes appear far apart, and the bridge of the broad nose is depressed. The palpebral fissures are narrow and the eyelids are swollen. The mouth is kept open and the thick broad tongue protrudes. The neck is short and thick, and there may be deposits of fat above the clavicles and between the neck and shoulders. The hands are broad and the fingers are short. Retardation in physical and mental development becomes evident by 3–6 months of age. The child had stunted growth and extremities are short. The degree of physical mental retardation increases with age. Social smile is delayed. Dentition and skeletal maturation are significantly delayed. Refractory anemia is common.

#### ESSENTIAL DIAGNOSTIC POINTS

- Growth retardation, diminished physical activities
- Impaired tissue perfusion
- Constipation
- Thick tongue, hoarseness
- Poor muscle tone
- Anemia, intellectual retardation
- Low thyroid hormone concentration
- TSH levels are elevated

#### CAUSES

- Thyroid dysgenesis
- Thyroid aplasia
- Thyroid hypoplasia
- Thyroid ectopy
- Thyroid dysmorphogenesis
- Resistance to thyroid-stimulating hormone
- Defect in thyroid hormone transport
- Resistance to thyroid hormone action
- Central hypothyroidism
- Transient hypothyroidism
- Thyroxine-binding globulin deficiency

**Acquired hypothyroidism:** It is caused mainly by lymphocytic thyroiditis, autoimmune thyroiditis, irradiation, the histiocytic infiltration of the thyroid and drugs. The drugs include iodine and amiodarone.

The clinical features include constipation, cold intolerance, increased need of sleep, delayed closure of epiphyses. Osseous maturation is delayed. This is an indication of the duration of hypothyroidism. Younger children will have pseudoprecocious puberty and galactorrhea. Head and visual problems are also noted. They usually have hyperplastic enlargement of the pituitary gland often with suprasellar extension. Sometimes only clinical evidence may be short stature. The ratio between the upper segment and lower segment is increased.

Growth changes include short stature, infantile skeletal proportions with relatively short extremities infantile naso-orbital configuration (bridge of nose flat, broad and underdeveloped, eyes seem to be widely spaced), delayed epiphyseal development, delayed closure of fontanelles and retarded dental eruption. Treatment of acquired hypothyroidism may not result in the predicted final adult target height. Menometrorrhagia may occur in older girls, and galactorrhea resulting from the stimulation of prolactin secretion or elevated thyrotropin-releasing hormone (TRH) has been reported.

#### GENERAL FEATURES

- Large baby
- Prolonged physiological jaundice
- Constipation
- Feeding problems
- Apneic episodes
- Noisy breathing
- Delayed dentition

### DIAGNOSIS

The diagnosis of primary hypothyroidism is confirmed by the presence of low serum  $T_4$  and elevated serum TSH values. Estimation of free  $T_4$  and  $FT_3$  is also available. TSH is an extremely sensitive index of primary hypothyroidism. Presence of thyroglobulin in the serum is also indicative of functioning thyroid tissue.

Thyroid antibody studies—antithyroglobulin (ATG) and antimitochondrial (AMA) or anti-peroxidase antibodies (APO) in particular—help in identifying autoimmune basis of the disease. Fine-needle aspiration cytology (FNAC) is helpful.

Initial investigations in a child with high TSH levels should include evaluation of radionuclide

uptake and thyroid ultrasound to confirm the presence of thyroid gland. If thyroid dysgenesis should be diagnosed if no thyroid tissue is visualized on ultrasound. Radiotracer uptake study with radioactive iodine or technetium should be done as soon as the diagnosis of primary congenital hypothyroidism has been established. Children with absent radiotracer uptake but normal thyroid on ultrasound could be suffering from defects in iodine transport, TSH receptor defects or trans-placental passage of TSH blocking antibody. Increased radioactive tracer uptake is indicative of iodine deficiency or dyshormonogenesis. Children with low TSH levels should be worked up for other pituitary defects.

Serum cholesterol and carotene are usually elevated in childhood but may be low or normal in infants. Cessation of therapy in previously treated hypothyroidism produces a marked rise in serum cholesterol levels in 6–8 weeks. Urinary creatinine excretion is decreased, and urinary hydroxyproline is low.

Circulating autoantibodies to thyroid constituents may be present. Serum growth hormone (GH) may be decreased, with subnormal human growth hormone (hGM) response to insulin-induced hypoglycemia and arginine stimulation in children with severe primary hypothyroidism.

### Radiograph

Retardation of osseous development can be shown radiographically at birth in approximately 60% of congenitally hypothyroid infants and indicates some deprivation of thyroid hormone during intrauterine life. The distal femoral and proximal tibial epiphyses, normally present at birth, are often absent. In undetected and untreated patients, the discrepancy between chronologic age and osseous development increases. The epiphyses often have multiple foci of ossification. Deformity (beaking) of the 12th thoracic or 1st or 2nd lumbar vertebra is common. X-rays of the skull show large fontanels and wide sutures. intersutural (Wormian) bones are common. The sella turcica is often enlarged and round; in rare instances, there may be erosion and thinning. Formation and eruption of teeth can be delayed. Cardiac enlargement or pericardial effusion may be present.

Skeletal maturation (bone age) is delayed. Centers of ossification, especially of the hip, may show multiple small centers or a single stippled, porous or fragmented center (epiphyseal dysgenesis). Vertebrae may show anterior beaking. Coxa vara and coxa plana may occur.

## Electrocardiogram

The electrocardiogram may show low-voltage P and T waves with diminished amplitude of QRS complexes and suggest poor left ventricular function and pericardial effusion. ECHO cardiography can confirm a pericardial effusion. The electroencephalogram often shows low voltage. In children older than 2 years of age, the serum cholesterol is usually elevated. Cardiac enlargement or pericardial effusion may be present. The electrocardiogram may show low voltage P and T waves with diminished amplitude of QRS complex. The electroencephalogram shows low voltage.

Scintigraphy with radioactive iodine may help to identify the etiology. FNAC is useful if thyroid continues to grow in spite of L-thyroxine.

### LABORATORY SALIENT FINDINGS

- $FT_3$  and  $FT_4$  levels are decreased
- Serum TSH levels are elevated
- Serum cholesterol and carotene are raised
- Serum GH may reduced
- Urinary creatinine excretion is decreased
- Bone age is delayed
- Cardiomegaly is common

## Screening Programs for Neonatal Hypothyroidism

Congenital hypothyroidism should be diagnosed by neonatal screening within 10 days of birth. It may be recognized clinically during the 1st month of life or may be so mild that it remains unrecognized clinically for months. Adequate treatment started as soon as possible—but certainly before the end of the 1st month of life—gives a better prognosis with respect to intellectual performance later in life.

Blood is collected onto filter paper and sent to a centralized laboratory for testing. The initial test performed varies among states:

- Initial TSH assay
- Initial thyroxine ( $T_4$ ) assay, with follow-up TSH if the  $T_4$  is  $<10\%$ .
- Simultaneously TSH-and  $T_4$ , is done which is the most optimal method.

It is advisable that each practicing general pediatrician and pediatric subspecialist should know their own state's method in order to be able take into account possible limitations. Regardless of method, the vast majority of infants with primary hypothyroidism are detected. However, each method has its disadvantages. Initial TSH assay tends to miss central hypothyroidism or

infants with delayed primary hypothyroidism in whom TSH rises later. Initial TSH testing tends to detect subclinical hypothyroidism.

## Evaluation and Diagnosis

Infants with abnormal newborn screening results need to be brought in to the pediatrician urgently. At this visit, besides physical examination, the infant should have the following blood work done: TSH, total T, and free T. The decision for treatment is based on these results. If these results confirm congenital hypothyroidism, the infant should be started on treatment and referred to a pediatric endocrinologist.

Patients with elevated serum TSH and low T, and free T, levels have primary congenital hypothyroidism, and treatment needs to be started immediately.

Patients with elevated TSH but normal total T, and free T, levels have subclinical hypothyroidism. This can be caused by an ectopic or hypoplastic thyroid gland or dys hormonogenesis. One can monitor these infants with serial blood tests for a few weeks; however, if the TSH does not normalize after 4 weeks of life, it is appropriate to initiate treatment in order to not compromise brain development.

Patients with a low or normal serum TSH and low total and free T, have central hypothyroidism. These infants need to be evaluated for adrenal insufficiency (among other pituitary hormones) prior to initiating treatment with thyroid hormone. If adrenal insufficiency is present and thyroid hormone treatment is initiated, these patients may go into adrenal crisis.

Patients with normal TSH, normal free T, but low total T, likely have TBG deficiency. TBG deficiency is an X-linked recessive disorder, occurring in 1 in 4000 newborns, predominantly males. This condition does not need treatment.

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes Turner's syndrome, Down's syndrome, gargoylism and Pendred's syndrome.

## TREATMENT

Levothyroxine ( $L-T_4$ ) given orally is the treatment of choice. The recommended initial starting dose (**Table 1**) is 10–15  $\mu\text{g}/\text{kg}/\text{day}$  (totaling 37.5–50.0  $\mu\text{g}/\text{day}$  for most term infants). The starting dose can be tailored to the severity of hypothyroidism. Rapid normalization of thyroid functions been

**TABLE 1:** Initial dose of levothyroxine.

Age	Levothyroxine dose ( $\mu\text{g/kg/day}$ )
0–3 Months	10–15
4–6 Months	8–10
7–12 Months	6–8
1–5 Years	5–6
6–12 Years	4–5
12 Years/puberty incomplete	2–3
12 Years/puberty complete	1.7

demonstrated to be important in achieving optimal neurodevelopmental outcome. Newborns with more severe hypothyroidism as judged by a serum  $T_4 < 5$  mU/L and/or imaging studies confirming aplasia, should be started at the higher end of the dosage range.

Levels of serum  $T_4$  or free  $T_4$  and TSH should be monitored at recommended intervals (every 1–2 months in the first 6 months of life, and then every 2–4 months between 6 months and 3 years of age). The goals of treatment are to maintain the serum free  $T_4$  or total  $T_4$  in the upper half of the reference range for serum TSH in the reference range for age, optimally 0.5–2.0 mU/L. The dose of L- $T_4$  on a weight basis gradually decreases with age.

Na-L-thyroxine is the treatment of choice for juvenile hypothyroidism. The initial dosage is based on age and adjusted to maintain serum TSH in the normal range. In central hypothyroidism, serum TSH is not a reliable euthyroid marker, and serum  $T_4$  should be maintained in the upper half of the normal range for age.

Delay in diagnosis, failure to correct initial hypothyroxinemia rapidly, inadequate treatment, and poor compliance in the first 2–3 years of life result in variable degrees of brain damage. Without treatment, affected infants are profoundly intellectually challenged and growth retarded. When onset of hypothyroidism occurs after 2 years of age, the outlook for normal development is much better even if diagnosis and treatment have been delayed, indicating how much more important thyroid hormone is to the rapidly growing brain of the infant.

## PROGNOSIS

Prognosis without treatment leads to mentally deficit dwarfs. The treatment with thyroid hormone results in linear growth, osseous maturation and sexual development. Infants detected and started with treatment in the 1st month of life will have normal IQ at 6 years.

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# Precocious Puberty

## PRESENTING COMPLAINTS

A 6-year-old boy was brought with the complaints of:

- Early development of secondary sexual characters since 6 months
- Large penis since 6 months
- Frequent erection since 6 months

## History of Presenting Complaints

A 6-year-old boy was referred to the hospital because of early development of secondary sexual characters. Father had noticed that the size of penis of his son was bigger over the last 6 months. Father had also noticed that his son was having frequent erection and he had developed pubic hair.

## Past History of the Patient

He was the eldest sibling of nonconsanguineous marriage. He was delivered at full term by normal

delivery. His birth weight was 3 kg. There was no significant postnatal event. He was bottle-fed since birth. His developmental milestones were normal, child had been completely immunized.

At the time of joining the play home, i.e., at the age of 3 years he was of the average height. Later his parents noted that he seemed to grow excessively and always was in need of new shoes. By the age of 6 years, he was tallest in class. Neither the teacher nor the parents noted any change in behavior. His health was generally good apart from several episodes of acute otitis media in infancy. He used to complain of headache occasionally.

He had 3-year-old sister who was normal. There was no family history of sexual precocity or hyperthyroidism.

## EXAMINATION

He was a tall muscular boy. He was well nourished. Anthropometric measurements included, the height was 129 cm (>97th centile), the weight was 22 kg (75th centile). Pubic and axillary hair were present. There was single circular café-au-lait spot of 5 mm in diameter on his left arm. Acne were present.

He was afebrile. The pulse rate was 96 per minute and respiratory rate was 20 per minute. Blood pressure recorded was 100/80 mm Hg. There was no pallor, no lymphadenopathy and no cyanosis.

Secondary sexual characters were present. His penis was big. The testes were 2 mL in volume and equal in size and consistency. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 11.8 g/dL
TLC	: 5,800 cells/cu mm
ESR	: 26 mm in 1st hour
LH level	: 6 U/L (Normal range: 0.2–4.9 U/L)
FSH level	: 5 U/L (Normal range: 1.8–3.2 U/L)

### CASE AT A GLANCE

#### Basic Findings

Height	: 129 cm (>97 centile)
Weight	: 22 kg (75th centile)
Temperature	: 37°C
Pulse rate	: 96 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 100/80 mm Hg

#### Positive Findings

##### History

- Bigger penis
- Erection
- Pubic hair
- Physical growth was faster

##### Examination

- Full muscular boy
- Acne, pubic and axillary hair
- Single café-au-lait spot

##### Investigation

- Plasma 17-OH progesterone: Raised
- Plasma DHEA sulfate: Raised
- Plasma androsterone: Raised



Plasma 17-OH progesterone	: 2.05 nmol/L (Normal range: <0.32–1.05 nmol/L)
Plasma DHEA sulfate	: 4.00 nmol/L (Normal range: 1.09–2.83 nmol/L)
Plasma androsterone	: 5.3 nmol/L (Normal range: 1.74–3.48 nmol/L)
Abdominal ultrasound	: Normal

## DISCUSSION

A 6-year-old boy had rapid growth and penile enlargement. Physical examination revealed acne, pubic and axillary hair. These findings are consistent with activation of the hypothalamus, pituitary and gonadal axis—true precocious puberty. It can also be due to exogenous androgens—pseudoprecocious puberty.

Precocious puberty is defined by the onset of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. The variation in the age of the onset of puberty in normal children, particularly of different ethnicities, makes this definition somewhat arbitrary (**Figs. 1 and 2**).

Genetic and environmental factors affect the onset of the puberty. The course is extremely variable. The tendency for the early onset of puberty is present in case of constitutional precocity. Congenital adrenal hyperplasia is autosomal recessive, while associated neurofibromatosis and tuberous sclerosis are inherited as autosomal dominant disorders are the causes of precocious puberty.

Depending on the primary source of the hormonal production, precocious puberty may be classified as central (also known as gonadotropin dependent, or true) or peripheral (also known as gonadotropin independent or precocious pseudo-puberty). The mixed type of precocious puberty occurs commonly in conditions such as congenital adrenal hyperplasia, McCune-Albright syndrome, and familial male-limited precocious puberty, when the bone age reaches the pubertal range (10.5–12.5 years).

In girls, fluctuating pubertal development and vaginal bleeding due hyperestrogenic state is common. The condition is usually self-resolving and there is no treatment. Recurrent ovarian cyst-McCune-Albright syndrome, somatic activating mutation of stimulatory G protein, skeletal [multiple fibrous dysplasia] and endocrine abnormalities (hyperthyroidism, rickets, and growth hormone



**Fig. 1:** True precocious puberty—male.



**Fig. 2:** Precocious puberty—female.

(GH) excess]. Delayed bone age and growth are characteristics.

In boys, this is caused by increase androgen production by testis and adrenals, with prepubertal luteinizing hormone (LH) levels. Adrenal overproduction due to congenital adrenal hyperplasia (CAH) is the chief cause of peripheral precocious puberty in boys. Human chorionic gonadotropin (hCG) secreting tumors of the liver, mediastinum or brain may present with peripheral precocious puberty.

## Central Precocious Puberty (Gonadotropin-dependent)

Central precocious puberty is defined by the onset of breast development before the age of 8 years in

girls and by the onset of testicular development (volume >4 mL) before the age of 9 years in boys, as a result of the early activation of the hypothalamic-pituitary-gonadal axis. It occurs 5–10 folds more frequently in girls than in boys and is usually sporadic. Central precocious puberty is always isosexual and stems from hypothalamic-pituitary-gonadal activation with ensuing sex hormone secretion and progressive sexual maturation.

True central precocious puberty (CPP) results from an increase in gonadotropin-releasing hormone (GnRH) secretion at a younger age than normal. Most cases are idiopathic, but given that organic causes include brain tumors, further evaluation is typically indicated. Hypothalamic hamartoma, neuronal migration defects, craniopharyngioma, hydrocephalus and tubercular meningitis are important causes. These disorders are associated with increased in testicular volume and elevated basal and GnRH-stimulated LH. Precocious puberty occurs more frequently among girls than among boys, but central nervous system (CNS) tumor as a cause of precocious puberty is more common among boys than among girls.

### Idiopathic Central Precocious Puberty

If no CNS tumor or additional diagnosis is determined, and if no family tendency toward early puberty exists, idiopathic CPP is diagnosed. This is a diagnosis of exclusion in which patients manifest all of the endocrine findings of normal puberty, but at an earlier age. Progress may be slow and continuous or waxing and waning. Girls are more frequently affected than boys.

### Central Nervous System Disorders

Hamartomas of the tuber cinereum are the most common CNS lesions causing CPP. They are composed of ectopic hypothalamic tissue, which usually contains GnRH in its neurons; thus, the hamartoma functions as a supplemental hypothalamus that operates outside of the normal inhibitory effects of the CNS on GnRH secretion. They do not enlarge and are not associated with a mass effect, but they can be associated with gelastic or laughing seizures, petit mal seizures, or grand mal seizures. They have a characteristic nonenhancing appearance on magnetic resonance imaging (MRI), so biopsy is rarely required.

Elevated intracranial pressure caused by hydrocephalus or a subarachnoid cyst can cause precocious puberty, which is reversed by release of the elevated intracranial pressure. Fetal or

childhood CNS infections, such as tuberculosis and brain abscess, can cause precocious puberty, as can cerebral vascular accidents and CNS trauma (including birth trauma). Developmental delay from various causes, including static cerebral encephalopathy, can cause precocious adrenarche or complete CPP. Congenital defects of the CNS such as septo-optic dysplasia may cause CPP.

### Additional Causes of CPP

Exposure to high serum concentrations of sex steroids leads to early maturation of the hypothalamic-pituitary axis with CPP even after the primary cause of increased exposure is treated. This may occur after glucocorticoid treatment is initiated for long-untreated virilizing congenital adrenal hyperplasia. Likewise, children with androgen-secreting tumors that are removed after years of virilization can subsequently have true CPP.

Although approximately 90% of girls have an idiopathic form, a structural central nervous system abnormality can be demonstrated in up to 75% of boys with central precocious puberty.

- *Evidence of a central nervous system mass:* Examination of optic fundus for possible increased intracranial pressure; visual fields testing for evidence of optic nerve compression by a hypothalamic or pituitary mass.
- *Evidence of androgenic influence:* Presence of acne and facial and axillary hair; increased muscle bulk and definition; extent of other body/pubescent hair; in boys increased scrotal rogradation accompanied by thinning and pigmentation of penile elongation; in girls clitoromegaly.
- *Evidence of estrogenic influence:* Size of breast tissue and nipple/areolar contouring; vaginal mucosa color (increased estrogen causes cornification of vaginal epithelium with color change from prepubertal shiny red to more opalescent pink); labia minora (become more prominent and visible between the labia majora as puberty progresses).
- *Evidence of gonadotropic stimulation:* Testicular enlargement >2.5 cm in length or >4 mL in volume (preferably measured using a Prader orchidometer of labeled volumetric beads); pubertal development without testicular enlargement usually suggests adrenal pathology.
- *Evidence of other mass:* Asymmetric testicular enlargement; hepatomegaly; abdominal mass.

## Peripheral Precocious Puberty (Gonadotropin-independent)

In peripheral precocious puberty, some of the secondary sex characteristics appear, but there is no activation of the normal hypothalamic-pituitary-gonadal interplay. In this latter group, the sex characteristics may be isosexual or heterosexual (contrasexual). Peripheral precocious puberty can induce maturation of the hypothalamic-pituitary-gonadal axis and trigger the onset of central puberty.

Unregulated sex steroid secretion is the major cause of peripheral precocious puberty in both sexes, although boys with hCG-secreting tumors will also have peripheral precocious puberty since the hCG stimulates the testes to produce testosterone. Laboratory analysis in peripheral precocious puberty reveals elevation in testosterone or estrogen and low or suppressed levels of pituitary gonadotropins. However, elevation of hCG (which would cause a positive pregnancy test) occurs in the case of ectopic hCG secretion. The only tissues that can secrete sex steroids are the gonads and adrenal glands, which are the final common pathways to sex steroid secretion.

### Boys

The hCG-secreting tumors can lead to sexual precocity, since high levels of hCG will stimulate the LH receptor, leading to gonadotropin-independent increases in testosterone secretion. hCG does not stimulate the seminiferous tubules, so testicular enlargement is less than occurs with normal puberty or CPP. hCG-secreting tumors include germ cell tumors (such as seminomas, dysgerminomas, yolk sac tumors, and teratomas) and hepatoblastomas and hepatomas. Boys with 47,XXY Klinefelter syndrome have an increased incidence of hCG-secreting mediastinal germ cell neoplasms.

Virilizing CAH due to 21-hydroxylase or 11-beta-hydroxylase deficiency will result in excessive androgen secretion. In boys, untreated CAH causes virilization without testicular enlargement, due to androgen secretion solely from the adrenal glands. Because gonadotropins are suppressed, the testes can be small for age or for the degree of virilization. The classical form manifests during infancy in males with normal male genital appearance but salt loss occurring in about 50% of cases. Without salt loss, the condition can present as GnRH-independent isosexual precocity in boys later in infancy. Additionally,

a testicular adrenal rest tumor (TART) composed of adrenocorticotrophic hormone (ACTH)-responsive tissue located in the testes (a common ectopic location for adrenal tissue) may enlarge in individuals with CAH, usually in teenagers or adults, resulting in a testicular mass and excessive androgen secretion.

Virilizing adenomas and carcinomas of the adrenal gland secrete large amounts of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS), which is peripherally converted to more potent androgens. When the adrenal gland is the cause of the virilization, the testes remain prepubertal in size. Leydig cell tumors are rare among boys but manifest as irregular enlargement of testis or, more rarely, both testes.

Premature Leydig and germinal cell maturation (or male limited precocious puberty or testotoxicosis) is a rare, self-limited dominant condition of boys. Often, a family history of affected fathers or uncles can be determined. The condition results from an activating mutation in the 7-transmembrane domain of the LH receptor, rendering it constitutionally activated such that it constantly stimulates testosterone production even in the absence of LH. Affected boys will virilize but have only minimal enlargement of the testes because there is predominant stimulation of Leydig cells and relatively less enlargement of the seminiferous tubules.

Familial cortisol resistance syndrome leads to a compensatory increase in ACTH secretion, which increases glucocorticoid secretion; because there is resistance to glucocorticoids, there is no manifestation of excess glucocorticoid effect despite elevated circulating glucocorticoids. However, because there is an increase in ACTH, adrenal androgen secretion rises, causing premature adrenarche and virilization.

### Girls

*Gonadotropin-independent:* Isosexual precocity among girls can be caused by ovarian cysts or neoplasms, exposure to exogenous estrogens, or abnormalities of the adrenal glands. Serum gonadotropin concentrations are suppressed, while serum estradiol levels are elevated. Prepubertal girls normally have small ovarian follicular cysts, but some cysts enlarge and secrete sufficient estrogen to cause breast development and even withdrawal bleeding. The estrogen levels are usually at pubertal values, but occasionally very high levels characteristic of tumors are encountered.

Occasionally, recurrent cyst formation can occur. Surgical resection is rarely indicated.

Several neoplasms can cause gonadotropin-independent isosexual precocity among girls. Granulosa cell tumors of the ovary are rare but can be discovered by bimanual examination. Gonadoblastomas can arise in streak gonads found in gonadal dysgenesis and secrete estrogen or even testosterone. These tumors are benign but can harbor malignant ovarian tumors. Estrogen-secreting adrenal neoplasms are infrequent compared with those that secrete androgens. Tumors that secrete hCG cause no physical pubertal changes in girls due to endocrine effects alone as hCG is the biological equivalent to LH in its activity and does not stimulate estradiol secretion.

### **Causes of GnRH-independent Sexual Precocity among Boys and Girls (Mixed)**

McCune-Albright syndrome (MAS) involves the triad of café-au-lait macules, polyostotic fibrous dysplasia of the skeleton and autonomous endocrine function, caused by activating mutations of the stimulatory G-protein subunit of the adenylyl cyclase system. Because these are somatic cell mutations that are not in the germline, the disease affects some organs while skipping others, leading to the variable manifestations. Patients may have autonomous hyperactivity of the somatotropes (acromegaly or gigantism), thyroid cells (thyrotoxicosis), parathyroid glands, adrenal glands (Cushing syndrome), and/or gonads. Precocious puberty is the most common endocrine finding and results from a constitutively active LH receptor.

Van Wyk-Grumbach syndrome is characterized by severe hypothyroidism, delayed bone age, and sexual precocity with reversal to a prepubertal state following thyroid hormone replacement therapy. It appears to be due to the cross-reaction of the elevated thyroid-stimulating hormone (TSH) on follicle-stimulating hormone (FSH) receptors. Girls may have breast development and menstrual flow, and boys may have enlargement of the testes as the result of enlargement of the seminiferous tubules. Because of the severe hypothyroidism, these patients may present with precocious puberty but will paradoxically have a delayed bone age. The pituitary gland may enlarge and erode the sella turcica in a manner incorrectly suggesting a tumor because of increased TSH secretion and thyrotroph hyperplasia. Once hypothyroidism is controlled, sexual precocity reverts and the sella turcica becomes smaller.

Peutz-Jeghers syndrome is an autosomal dominant condition characterized by intestinal hamartoma and polyp formation in association with a distinctive pattern of skin and mucosal hyperpigmentation. Cancer incidence is increased, including gonadal tumors, which may result in sexual precocity in children.

## **A CLASSIFICATION SCHEME FOR PRECOCIOUS PUBERTY**

### **Central (or Complete) Isosexual Precocious Puberty (GnRH-dependent Sexual Precocity or Premature Activation of the Hypothalamic Pulse Generator)**

- Familial or constitutional central precocious puberty
- Idiopathic true precocious puberty
- *CNS tumors:*
  - Hamartoma of the tuber cinereum
  - Optic glioma
  - Hypothalamic astrocytoma
  - Craniopharyngioma
  - Ependymoma
- *Other CNS disorders:*
  - Encephalitis
  - Static encephalopathy
  - Brain abscess
  - Sarcoid or tubercular granuloma
  - Head trauma
  - CNS surgery
  - Hydrocephalus
  - Arachnoid cyst
  - Myelomeningocele
  - Vascular lesion
  - Cranial irradiation

### **Peripheral (or Incomplete) Isosexual Precocity (Hypothalamic GnRH-independent)**

- *Boys:*
  - Gonadotropin-secreting tumors
  - hCG-secreting —CNS tumor
  - Increased androgen production by the adrenal gland or testes
  - CAH (CYP21 and CYP11B1 deficiency)
  - Virilizing adrenal neoplasm
  - Leydig cell adenoma
  - Premature Leydig and germ cell maturation (testotoxicosis)
  - Cortisol resistance syndrome
- *Girls:*
  - Ovarian cyst
  - Estrogen-secreting ovarian or adrenal neoplasm

- *Both sexes:*
  - McCune-Albright syndrome
  - Peutz-Jeghers syndrome
  - Severe primary hypothyroidism
  - Exogenous exposures.

## CLINICAL FEATURES (FIG. 3)

### Boys

In boys, there will be enlargement of pubis and testes, appearance of pubic hair, acne and frequent erections occur. Voice deepens and linear growth is accelerated.

In precocious development, increases in growth rate and growth of pubic hair are the common presenting signs. Testicular size may differentiate true precocity, in which the testes enlarge, from pseudoprecocity (most commonly due to congenital adrenal hyperplasia), in which the testes usually remain small. There are some exceptions, e.g., testicular enlargement may occur in pseudoprecocity of long-standing due to secondary activation of central precocity from prolonged elevation of androgen levels. Tumors of the testes are associated with asymmetric testicular enlargement.

A boy who exhibits symmetrically enlarging testes of homogeneous consistency is likely to have CPP. Patients with gonadotropin-independent Leydig and germ cell maturation tend to have a small degree of testicular enlargement, while boys with adrenal androgen excess (as in the case of enzyme defects or tumors) or an exogenous androgen source will have nonenlarging testes. Laboratory evaluation will reveal elevated

testosterone and gonadotropin levels in CPP, while gonadotropins will be low or prepubertal in peripheral precocious puberty. If testosterone is elevated but gonadotropins are suppressed, an hCG-secreting tumor is possible and  $\beta$ -hCG should be measured. The modern  $\beta$ -hCG assay does not cross-react with LH. MRI should subsequently be invoked to determine the tumor location.

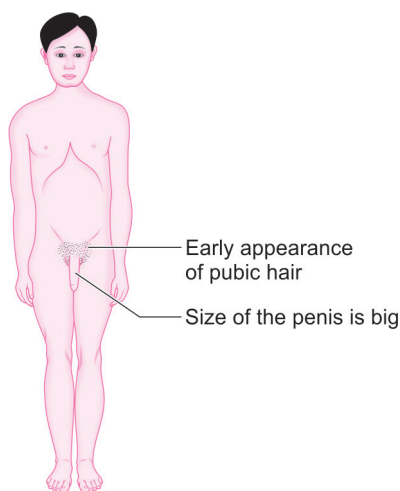
### Girls

Sexual development may begin at any age and generally follows the sequence observed in normal puberty. In girls, early menstrual cycles may be more irregular than they are with normal puberty. The initial cycles are usually anovulatory, but pregnancy has been reported. In boys, testicular biopsies have shown stimulation of all elements of the testes, and spermatogenesis has been observed. In affected girls and boys, height, weight, and osseous maturation are advanced. The increased rate of bone maturation results in early closure of the epiphyses, and the ultimate stature is less than it would have been otherwise.

Although the clinical course is variable, three main patterns of pubertal progression can be identified. Most girls (particularly those younger than 6 years of age at the onset) and a large majority of boys have rapidly progressive puberty, characterized by rapid physical and osseous maturation, leading to a loss of height potential. An increasing percentage of girls (older than 6 years of age at the onset) with an idiopathic form have a slowly progressive variant, characterized by parallel advancement of osseous maturation and linear growth, with preserved height potential. Spontaneously regressive or unsustained central precocious puberty is quite rare. This variability in the natural course of sexual precocity underscores the need for longitudinal observation at the onset of sexual development, before treatment is considered.

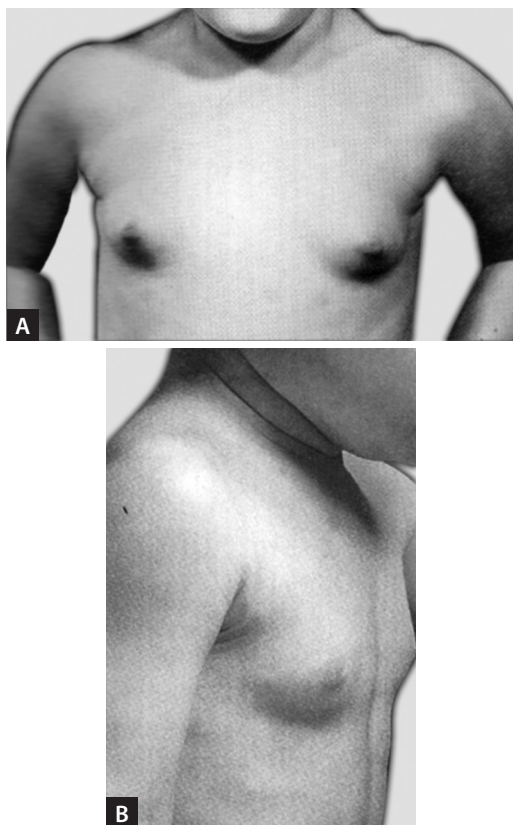
In the girls, the first sign is the development of breast. Pubic hair may appear simultaneously and more often appears later. Development of external genitalia, appearance of axillary hair and onset of menstruation follow. The initial cycles are anovulatory.

A girl with early breast development may have premature thelarche (Figs. 4A and B), CPP; or gonadotropin-independent peripheral precocious puberty. If pubic hair development is present in appropriate amount for the degree of



**Fig. 3:** Clinical features.





**Figs. 4A and B:** (A) Thelarche; (B) Premature thelarche.

breast development, then CPP is likely. Laboratory evaluation begins with measurement of high sensitivity basal or GnRH stimulated levels of LH. If the LH is pubertal, central causes of precocious puberty are considered, and cranial magnetic MRI is usually indicated. If LH is not pubertal, serum estradiol levels are measured. If serum estradiol is not elevated, a diagnosis of premature thelarche is made. If elevated, an ultrasound of the uterus and ovary should be performed.

In practice, most providers obtain FSH, LH, and estradiol levels simultaneously to expedite the workup and minimize number of blood draws.

#### GENERAL FEATURES

##### Girls:

- Breast enlargement
- Early appearance of pubic hair

##### Boys:

- Enlarged penis
- Increased testicular size

A girl with early pubic hair without concurrent breast development may have benign premature

adrenarche, late-onset congenital adrenal hyperplasia, or a virilizing tumor. The evaluation begins with determination of DHEAS levels. If significantly elevated, virilizing adrenal tumors need to be considered.

In both girls and boys, height, weight and bone maturity is advanced. The increased rate of ossification results in early closure of the epiphyses.

## DIAGNOSIS

A detailed history and clinical evaluation are helpful in arriving at a diagnosis and directing investigations.

Aims of evaluation include confirmation of diagnosis, identification of underlying etiology and determination of prognosis and treatment.

*Clinical:* History should include the onset, progression and extent of puberty. Idiopathic CPP usually presents between 6 and 7 years of age. The earlier the onset, the greater is the likelihood of an underlying organic cause. Hypothalamic hamartoma and familial testotoxicosis present very early in the first 3 years of life. Exposure to steroids, estrogens and androgens should be enquired.

Family history of precocious puberty and early menarche points towards idiopathic central precocious puberty. Features of hypothyroidism should be assessed. Advanced growth is characteristic of precocious puberty; growth retardation indicates hypothyroidism or concomitant GH deficiency.

Examination of vaginal mucosa for estrogen effect provides clues regarding the pubertal status of the patient. Red, glistening mucosa suggests lack of estrogens while pink mucosa with mucus is indicative of estrogen effect. Abdominal examination for adrenal or ovarian mass should be done. Features of McCune-Albright syndrome include café-au-lait spots, polyostotic fibrous dysplasia, bony deformities and polyendocrinopathy.

*Pubertal progression:* In idiopathic CPP, the rate of progression may sometimes be very slow with menarche occurring up to 5 years after breast development. Rapid progression of puberty is seen in androgen producing tumors, ovarian cysts and some CNS minors such as hypothalamic hamartoma.

Accelerated growth is a feature of both central and peripheral precocious puberty but is not seen in pubertal variants. Irregular vaginal bleeding is more common in functioning ovarian tumors and hypothalamic hamartoma. Past history of CNS

infection suggested by headaches, visual disturbances, personality changes, developmental delay and seizures would suggest a neurologic disorder.

**Investigations:** Assessment of pubertal status is based on basal or stimulated gonadotropin levels. Pooled gonadotropin levels are preferred due to their pulsatile secretion. LH is a better indicator compared to FSH as LH levels increase significantly during puberty. LH levels in the pubertal range with LH/FSH ratio more than one is suggestive of development of puberty.

It is recommended that all boys with precocious pubertal development and all girls with the following features should be evaluated for the mechanism and potential for progression of puberty:

- Precocious puberty stage 3 or higher
- Stage 2 with additional criteria such as increased growth velocity
- Evidence of CNS dysfunction or PPP

#### **Hormonal evaluation:**

- **Sex steroids:** In girls *serum estradiol* levels are not very helpful in determining the stage of puberty. Levels overlap between normal pre-puberty, early puberty, precocious puberty and premature thelarche. Levels greater than 20 pg/mL suggest that puberty has started. Markedly elevated levels (>100 pg/mL) are seen in estrogen secreting ovarian tumors and sometimes in follicular cysts.

In boys, *serum testosterone* levels less than 30 ng/mL are generally prepubertal, though in some laboratories levels of 10–30 ng/mL may indicate early puberty. Testosterone levels may be very high related to the stage of puberty in boys with primary gonadotropin excess.

- **Serum gonadotropins:** Gonadotropin levels are elevated in CPP and suppressed in PPP. Basal serum FSH and LH are of limited value in early puberty. But random LH estimated by sensitive third-generation assays is a good screening test for CPP. A level of less than 0.1 IU/L is prepubertal and 0.3 IU/L or more is pubertal. Random FSH levels are not helpful in discriminating between prepubertal and pubertal children.
- **GnRH stimulation tests** more helpful in distinguishing CPP from PPP. In CPP an LH predominant response is seen. An increase in FSH levels much more than LH indicates that the child is prepubertal. In PPP, gonadotropin levels do not rise in response to GnRH stimulation.

- **Serum DHEAS** levels are elevated in premature adrenarche and can be very high in virilizing adrenal problems.
- **Serum 17-hydroxyprogesterone (17-OHP)** and the response to ACTH or serum 11-deoxycortisol may be required to rule out CAH.
- **Serum hCG** levels, if an hCG-secreting tumor is suspected in boys.
- **Thyroid hormone** studies in suspected hypothyroidism.

#### **Radiology:**

- **Bone age:** Skeletal maturation is advanced in all cases of precocious puberty, except if associated with hypothyroidism, but remains normal in the incomplete forms. It is also helpful in predicting adult height.
- **CT or MRI of brain:** To determine the etiology of CPP.
- **Pelvic and abdominal sonography:** To evaluate the size and morphology of the uterus, ovaries and adrenals. This is essential in PPP to find the cause. In CPP the size of the uterus is increased (>2 mL in volume or >3.4 cm in length) and an endometrial shadow is seen. The ovaries will also be enlarged bilaterally, and may show multiple small follicular cysts.
- **Testicular sonography:** If a tumor is suspected.
- **Skeletal survey:** In suspected cases of McCune-Albright syndrome.
- **Advanced bone age:** More than 2 years ahead of chronological age suggestive of progressive precocious puberty, while normal bone age indicates slowly progressive puberty retarded growth and skeletal maturation is diagnostic of hypothyroidism. Pubertal LH levels are suggestive of gonadotropin-dependent precocious puberty and should be followed with an MRI of brain. Girls with prepubertal LH levels should undergo ultrasound of ovary and adrenals (for ovarian cyst and adrenal tumor) and skeletal survey (for fibrous dysplasia in McCune-Albright syndrome).

Basal serum LH and FSH concentrations are usually not in the pubertal range in boys with true sexual precocity, but the LH response to GnRH stimulation testing is pubertal (>10 IU/L). sexual precocity caused by congenital adrenal hyperplasia is usually associated with abnormal concentrations of DHEA, androstenedione, 17-hydroxyprogesterone (in congenital adrenal hyperplasia due to 21-hydroxylase deficiency), 11-deoxycortisol (in congenital adrenal hyperplasia due to 11-hydroxylase deficiency) or a combination of these steroids.

Serum hCG concentrations can identify the presence of an hCG-producing tumor (e.g., CNS dysgerminoma, hepatoma) in boys who present with apparent true sexual precocity (i.e., accompanied by testicular enlargement) but suppressed gonadotropins following LHRH.

#### LABORATORY SALIENT FINDINGS

- Increased LH response to GnRH stimulation test
- Abnormal plasma concentration of dihydroepiandrosterone, androstenedione, 17-hydroxyprogesterone
- Serum hCG, concentration may be elevated
- Ultrasonography is useful to detect hepatic, presacral and testicular tumors

### DIFFERENTIAL DIAGNOSIS

- Hypothyroidism
- McCune-Albright syndrome
- Virilizing tumor
- Granulosa cell tumor
- Congenital adrenal hyperplasia

### TREATMENT

Specific therapy should be provided whenever possible. Treatment of idiopathic true precocious puberty in boys is similar to that in girls. Treatment of McCune-Albright syndrome of familial Leydig cell hyperplasia with agents that block steroid synthesis (e.g., ketoconazole), with an anti-androgen (e.g., spironolactone) or a combination of both has been successful.

If the underlying cause is amenable to neurosurgery, it should be removed. Highly potent long acting analogue of GnRH are used. Triptorelin and leuprolide are depot preparations administered intramuscularly every month. GnRH analogue helps to increase the ultimate height.

The pseudoprecocious puberty is caused by estrogen producing granulosa cell tumor, congenital adrenal hyperplasia, McCune-Albright syndrome. Underlying cause should be treated.

Medroxyprogesterone acetate is given in the dose of 100 mg/m<sup>2</sup> every 2–3 months by intramuscular injection. Oral dose is 10 mg twice daily. Cyproterone acetate given in the dose of 75–100 mg/m<sup>2</sup>/day in 2–3 divided dose is helpful for stopping cyclical bleeding. Ketoconazole is also used to suppress peripheral gonadal hormone secretion.

Long-acting formulations of GnRH agonists, which maintain fairly constant serum concentrations of the drug for weeks or months, constitute the preparations of choice for treatment of central precocious puberty.

The available preparations include:

- Leuprolide acetate (Ld), in a dose of 0.25–0.3 mg/kg (minimum 7.5 mg) intramuscularly once every 4 weeks
- Longer-acting preparations of depot leuprolide, allowing for injections (11.25–30.0 mg intramuscularly) every 90 days
- Histrelin, a subcutaneous 50 mg implant with effects lasting 12 months.

Other preparations D-Trp-GnRH goserelin acetate are approved for treatment of precocious puberty. Recurrent sterile fluid collections at the sites of injections are an uncommon local side effect and occur in less than 1–3% of patients treated with depot leuprolide.

Other available treatment options, usually reserved for children who cannot tolerate the products listed above, include subcutaneous injections of aqueous leuprolide, given once or twice daily (total dose 60 µg/g/24 h), or intranasal administration of the GnRH-1 agonist nafarelin, 800 µg bid. The potential for irregular compliance with daily administration, as well as the variable absorption of the intranasal route for nafarelin, may limit the long-term benefit of the latter preparations on adult height.

Congenital adrenal hyperplasia is managed with hydrocortisone and fludrocortisone. Surgery is done for adrenal and testicular tumors, radiotherapy is effective in hCG-secreting tumors. Aromatase inhibitors and antiandrogens are indicated in testotoxicosis.

Treatment results in decrease of the growth rate, generally to age-appropriate values, and an even greater decrease of the rate of osseous maturation. Some children, particularly those with greatly advanced (pubertal) bone age, may show marked deceleration of their growth rate and a complete arrest in the rate of osseous maturation.

Treatment results in enhancement of the predicted height, although the actual adult height of patients followed to epiphyseal closure is approximately 1 SD less than their midparental height. In girls, breast development may regress in those with Tanner stages development. Most commonly, the size of the breasts remains unchanged in girls with stages III–V development, or may even increase slightly because of progressive adipose tissue deposition. The amount of glandular tissue decreases. Pubic hair usually remains stable in girls, or may progress slowly during treatment, reflecting the gradual increase in adrenal androgens. Menses, if present, cease. Isolated thelarche usually present around the

age of 1–2 years and show gradual regression by 5 years. Isolated adrenarche—premature development of pubic hair and acne in absence of breast development or menarche. Most of them are normal variants, does not require any treatment. Isolated menarche—vaginal bleeding without breast development requires evaluation of local causes (infection, foreign body, sexual abuse or tumors).

Pelvic sonography demonstrates a decrease of the ovarian and uterine size. In boys, there is decrease of testicular size, variable regression of pubic hair, and decrease in the frequency of erections. Except for a reversible decrease in bone density (of uncertain clinical significance), no serious adverse effects of GnRH analogs have been reported in children treated for sexual precocity. If treatment effective, the serum sex hormone concentrations decrease to prepubertal levels (testosterone, <10–20 ng/dL, in boys; estradiol, <5–10 pg/mL in girls).

Surgical management for endocrine purposes is not usually indicated, as the lesion is responsive to GnRH agonists. Surgery is advised for seizure. Management is sometimes indicated. CNS tumors can cause other symptoms, such as headache, abnormalities of vision, optic atrophy, and diabetes insipidus, and thus a thorough neurologic examination and review of systems

must be a part of the evaluation of a child sexual precocity.

Radiation therapy is most commonly associated with gonadotropin deficiency, but may also cause CPP even if the treated tumor does not cause precocious puberty. Higher doses of radiation may be more likely to cause GnRH deficiency, whereas lower doses may lead to CPP or hypogonadotropic hypogonadism. When radiation causes CPP, the resultant growth acceleration can mask radiation-induced GH deficiency. When both occur, treatment with combined GH and GnRH agonist may be necessary to achieve a normal range of adult height.

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# Undescended Testes

## PRESENTING COMPLAINTS

A 2-year-old boy was brought with the complaint of absence of testes since birth.

## History of Presenting Complaints

A 2-year-old boy was brought to the pediatric outpatient department of testes on the left side. His mother recollects her memory that she has noticed that at the time of the birth and brought that to the attention of the pediatrician. But the pediatrician assured and asked to wait till 1 year, and to consider the evaluation if it remains like that. The testis on the right side was present and normal in size. There was no history of other congenital anomalies.

## Past History of the Patient

He was the only sibling of consanguineous marriage. He was born at full term by normal delivery. He was on breast milk as soon as possible. He was on breast milk exclusively for first 4 months. Later weaning was started with advice of the family doctor. His developmental milestones were normal. He had been immunized completely.

## EXAMINATION

On examination, the child was moderately built and nourished. He was playing with toys on the examination table. He was unaware of the reason for which he was brought to the hospital. Anthropometric measurements included the height was 89 cm (>90 centile), and the weight was 12 kg (above 75th centile).

He was afebrile. The heart rate was 98 per minute and respiratory rate was 20 per minute. Blood pressure recorded was 60/46 mm Hg. The child was pale, there was no lymphadenopathy, no clubbing, and no edema.

Per abdomen examination revealed, soft abdomen with no organomegaly. There was absence of testes on the left side. Testis was present in the right side and normal in size. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 9 g/dL
TLC	: 9,800 cells/cu mm
ESR	: 26 mm in the 1st hour
AEC	: 440 cells/dL
X-ray abdomen	: Normal
Abdominal scan	: Revealed no significant finding

## DISCUSSION

Cryptorchism (undescended testes) is a common disorder in children. It may be unilateral or bilateral and may be classified as ectopic or true cryptorchism. Approximately 3% of term male newborns have an undescended testes at birth, with a higher proportion among premature infants, because testicular descent occurs at 7–8 months of gestation, 30% of premature male infants have an undescended testis; the incidence is 14% at term.

Spontaneous descent occurs secondary to a temporary testosterone surge during the first 2 months, which also results in significant penile growth. In over 50% of these patients, the testes

### CASE AT A GLANCE

#### Basic Findings

Height	: 89 cm (>90th centile)
Weight	: 12 kg (above 75th centile)
Temperature	: 36°C
Pulse rate	: 98 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 60/46 mm Hg

#### Positive Findings

##### History

- Absence of the testes

##### Examination

- Absence of the testis in the left scrotum

##### Investigation

- Normal



descend by the 3rd month, by age 1 year 80% of all undescended testes are in the scrotum. If the testis has not descended by 4 months, it will remain undescended. Cryptorchidism is bilateral in 10% of cases.

Secondary cryptorchidism follow the repair of inguinal hernia. Further descent may occur through puberty, the later perhaps stimulated by endogenous gonadotropins.

Cryptorchidism can occur in an isolated fashion or may be associated with other findings. Abnormalities in the hypothalamic-pituitary-gonadal axis predispose to cryptorchism. Androgen biosynthesis or receptor defects may also predispose to cryptorchidism and undervirilization.

Ectopic testes are presumed to develop normally but are diverted as they descend through the inguinal canal. They are sub-classified on the basis of their location. Surgery is indicated once the diagnosis is established.

The true undescended testis is found along normal paths of descent and processus vaginalis is usually patent. The ectopic testis has completed its course of descent through inguinal canal. But it ends up in subcutaneous location. The usual site is lateral to external inguinal ring, i.e., below the subcutaneous fascia.

Undescended testes are usually in inguinal canal. Ectopic testis is in superficial inguinal pouch or perineum. In a newborn, with bilateral nonpalpable testes, one should suspect virilized female with congenital adrenal hyperplasia (CAH). The diagnosis of bilateral cryptorchism in an apparently male newborn should never be made until ruling out the possibility that the child is actually a fully virilized female with potentially fatal salt-losing congenital adrenal hyperplasia.

## **PATHOGENESIS**

The process of testicular descent is regulated by an interaction between hormonal and mechanical factors, including testosterone, dihydrotestosterone, müllerian-inhibiting factor, the gubernaculum, intra-abdominal pressure, and the genitofemoral nerve. The testis develops at 7–8 weeks of gestation. At 10–11 weeks, the Leydig cells produce testosterone which stimulates differentiation of the wolffian (mesonephric) duct into the epididymis, vas deferens, seminal vesicle, and ejaculatory duct. At 32–36 weeks, the testis, which is anchored at the internal inguinal ring by the gubernaculum, begins its process of descent. The gubernaculum distends the inguinal canal and guides the testis into the scrotum.

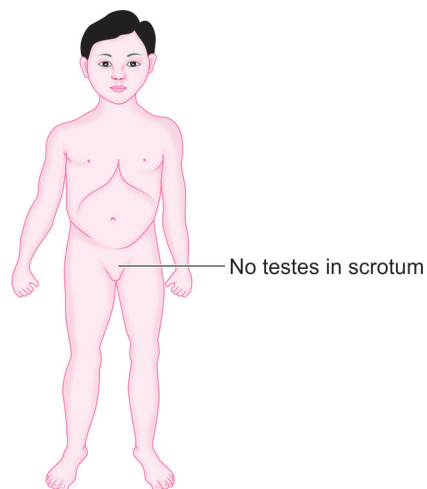
True cryptorchism is thought in most cases to be the result of dysgenesis. Cryptorchid testes frequently have a short spermatic artery, poor blood supply or both. Although early scrotal positioning of these testes will obviate further damage related to intra-abdominal location, the testes generally remain abnormal, spermatogenesis is rare, and the risk of malignant neoplasm is increased. These testes should probably be removed if spermatogenesis does not occur after a reasonable period of observation.

These are histologically normal at birth. By the end of 2nd year, the number of germ cells in the affected testis is severely reduced. Delayed germ cell maturation and number, hyalinization of seminiferous tubulus, reduced Leydig cell number are typical. These changes are progressive over time if testes remain undescended. Surgical correction at the early age results in greater possibility of fertility. The patient with cryptorchidism has 20–40% increased risk of malignant tumor in third or fourth decade.

## **CLINICAL FEATURES (FIG. 1)**

Undescended testes are classified as abdominal (nonpalpable), peeping (abdominal but can be pushed into the upper part of the inguinal canal), inguinal, gliding (can be pushed into the scrotum but retracts immediately to the pubic tubercle), and ectopic (superficial inguinal pouch or; rarely, perineal). Most undescended testes are palpable just distal to the inguinal canal over the pubic tubercle.

A disorder of sex development should be suspected in a newborn phenotypic male with



**Fig. 1:** Clinical features.

bilateral nonpalpable testes, as the child could be a virilized girl with congenital adrenal hyperplasia. In a boy with midpenile or proximal hypospadias and a palpable undescended testis, disorder of sexual development is present in 15% and the risk is 50% if the testis is nonpalpable.

The consequences of cryptorchidism include poor testicular growth, infertility, testicular malignancy, associated hernia, torsion of the cryptorchid testis, and the possible psychologic effects of an empty scrotum.

The undescended testis is normal at birth histologically, but pathologic changes can be demonstrated by 6–12 months. Delayed germ cell maturation, reduction in germ cell number, hyalinization of the seminiferous tubules, and reduced Leydig cell number are typical; these changes are progressive over time if the testis remains undescended. Similar, although less severe, changes are found in contralateral descended testis after 4–7 years. After treatment for a unilateral undescended testis, 85% of patients are fertile, which is slightly less than 90% rate of fertility in an unselected population of men. In contrast following bilateral orchiopexy, only 50–65% of patients are fertile.

Approximately 10% of undescended testes are nonpalpable testis. Of these, 50% are viable testes in the abdomen or high in the inguinal canal and 50% are atrophic or absent, almost always in the scrotum, secondary to spermatic cord torsion in utero (vanishing testis). If the nonpalpable testis is abdominal, it will not descend after 3 months of age. Although sonography often is performed to try to identify whether the testis is present, it rarely changes clinical management, because the abdominal testis and atrophic testis are not identified on sonography.

The risk of a germ cell malignancy developing in an undescended testis is four times higher than in the general population and is approximately 1 in 80 with a unilateral undescended testis and 1 in 40–50 for bilateral undescended testes. Testicular tumors are less common if the orchiopexy is performed before 10 years of age, but they still occur, and adolescents should be instructed in testicular self-examination. The peak age for developing a testis tumor is 15–45 years.

Retractile testes may be misdiagnosed as undescended testes. Boys older than age 1 year often have a brisk cremasteric reflex, and if the child is anxious or ticklish during scrotal examination, the testis may be difficult to manipulate into the scrotum. Boys should be examined with their legs in a relaxed frog leg position, and if the testis can

be manipulated into the scrotum comfortably, it is probably retractile. It should be monitored every 6–12 months with follow-up physical examinations because it can become an acquired undescended testis.

The most common tumor developing in an undescended testis in an adolescent or adult is a seminoma (65%); after orchiopexy, nonseminomatous tumors represent only 65% of testis tumors. Orchiopexy seems to reduce the risk of seminoma. Whether early orchiopexy reduces the risk of developing cancer of the testis is controversial, but it is uncommon for testis tumors to occur if the orchiopexy performed before the age of 2 years. The contralateral scrotal testis is not at increased risk of malignancy.

Plasma testosterone concentrations may be obtained after human chorionic gonadotropin (hCG) stimulation to confirm the presence or absence of abdominal testes. The child with bilaterally undescended testes should be evaluated for sex chromosome abnormalities; evaluation should include consideration of the possibility that the child is a virilized female.

#### LABORATORY SALIENT FINDINGS

- Concentration of testosterone after hCG stimulation test
- Chromosome analysis
- Ultrasonography of abdomen

Indirect inguinal hernia always accompanies undescended testes. It is important to differentiate true undescended testis from retractile or ectopic testis due to therapeutic and prognostic implications. Poorly developed scrotum and inability to bring down the testis to the scrotal sack suggests true descended testis. Retractable testis is an otherwise fully descended testis that has an active cremasteric reflex, which retracts it into the groin.

Penoscrotal hypospadias and genital ambiguity (**Fig. 2**) is suggestive of disorders of androgen production or action. The hCG stimulation test should be done in boys with bilateral nonpalpable testis to differentiate abdominal testis from anorchia.

#### GENERAL FEATURES

- Testes will be in inguinal canal
- Small scrotum
- Infertility in adult

### DIFFERENTIAL DIAGNOSIS

In palpating for the testes, the cremasteric reflex may be elicited, with a resultant ascent of the testes



**Fig. 2:** Penoscrotal hypospadias and genital ambiguity.

into the inguinal canal or abdomen (pseudo-cryptorchism). To prevent this, the fingers first should be placed across the abdominal ring and the upper portion of the inguinal canal, obstructing ascent.

Examination while the child is in the squatting position or in a warm bath is also helpful. No treatment for retractile testes is necessary and the prognosis for testicular descent and competence is excellent.

## TREATMENT

### Surgical Treatment

The congenital undescended testis should be treated surgically by 9–15 months of age. With anesthesia by a pediatric anesthesiologist, surgical correction at 6 months is appropriate, because spontaneous descent of the testis will not occur after 4 months of age. Most testes can be brought down to the scrotum with an orchiopexy, which involves an inguinal incision, mobilization of the testis and spermatic cord, and correction of an indirect inguinal hernia. In some boys with a testis that is close to the scrotum, a prescrotal orchiopexy can be performed. In this procedure, the entire operation is performed through an incision along the edge of the scrotum. Often the associated inguinal hernia also can be corrected with this incision. Advantages of this approach over the

inguinal approach include shorter operative time and less postoperative discomfort. The risk of malignancy is 4–10 times higher.

In boys with a nonpalpable testis, diagnostic laparoscopy is performed in most centers. This procedure allows safe and rapid assessment of whether the testis is intra-abdominal. In most cases, orchiopexy of the intra-abdominal testis located immediately inside the internal inguinal ring is successful, but orchiectomy should be considered in more difficult cases or when the testis appears to be atrophic. A two-stage orchiopexy sometimes is needed in boys with a high abdominal testis. Boys with abdominal testes are managed with laparoscopic techniques at many institutions.

Treatment of bilateral undescended testes is identical to the treatment of unilateral undescended testes when the testes are palpable. When testes are not palpable then the serum testosterone levels are measured before and after giving hCG. If testosterone level rises, abdominal exploration and orchidopexy should be undertaken.

### Hormonal Treatment

Gonadotropin therapy (hCG) has been used in the treatment for cryptorchism but is not generally successful. Hormone treatment can be useful in the identification and descent of retractile testes or to evaluate for the presence of testicular tissue. Various treatment regimens have been used, ranging from 250 to 1000 IU given twice weekly for 5 weeks and will generally cause descent of retractile testes.

Androgen treatment (e.g., depot testosterone) is indicated as replacement therapy in the male child who lacks functional testes beyond the normal age of puberty.

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## PRESENTING COMPLAINTS

An 8-year-old boy was brought with the complaints of:

- Fever since 3 days
- Pain in the joints since 2 days
- Skin rashes since 1 day

## History of the Presenting Complaints

Mother gave the history of fever since 3 days. Fever is of moderate to high degree associated with the child and rigor. Fever used to be more in the night. She also gave the history that his son has vomited. Boy also complained of pain in the joints, especially the small joint of the hand. Hence, he was finding difficulty in walking and eating by himself.

His mother noticed the rashes all over the body since 1 day. This led her to bring the child to the hospital. The rash were not pruritic. The boy was taking treatment for the presenting complaints.

### CASE AT A GLANCE

#### Basic Findings

Height	: 123 cm (50th centile)
Weight	: 25 kg (75th centile)
Temperature	: 38°C
Pulse rate	: 120 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 80/60 mm Hg

#### Positive Findings

##### History

- Fever
- Joint pain
- Skin rash

##### Examination

- Dehydrate
- Tender joints
- Swelling of the joints

##### Investigation

- ESR: Raised
- IgM antibodies: Raised

## Past History of the Patient

He was the elder sibling of nonconsanguineous marriage. He was born at term by normal vaginal delivery. There was no significant postnatal event. He was exclusively on breastfeeds for 6 months. Weaning was started as per the advice of the family doctor. The child was on family food by 15 months. He had been completely immunized. All the developmental milestones were normal. The performance at school was good. There was also history of similar type of illness in the school.

## EXAMINATION

The boy was moderately built and moderately nourished. There were signs of moderate dehydration. He was looking toxic and dehydrated. The anthropometric measurements included, the height was 123 cm (50th centile) and weight was 25 kg (75th centile).

He was febrile (38°C). The pulse rate was 120 per minute and respiratory rate was 26 per minute. The blood pressure recorded was 80/60 mm Hg. There were signs of dehydration. There was no pallor, no lymphadenopathy, cyanosis or icterus.

There were tenderness in the small joints of the hand and leg. There was swelling over the joints. The rashes were present over the body. Macular rashes were present. There was no itching. There was no organomegaly. Bowel sounds were regular. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 13 g/dL
TLC	: 9,800 cells/cu mm
DLC	: P <sub>67</sub> L <sub>30</sub> E <sub>2</sub> M <sub>1</sub>
ESR	: 30 mm in the 1st hour
AEC	: 320 cells/cu mm
X-ray chest	: NAD
IgM antibodies	: Positive

## DISCUSSION

It is an acute disease characterized by fever, arthritis and skin rash. This is caused by enveloped virus capable of replicating in mosquitoes.

The chikungunya transmission involves *Aedes africanus*, *A. fuscifer* and wild primates. This is seen among rural population. In urban population the cycle involves *A. aegypti* and humans. Outbreaks typically occur during the rainy season. This is associated with the population density of the mosquito vector. These breed in household containers and puddles with peak activity in mid-morning and late afternoon. The disease typically vanishes for years after the epidemics because of the development of immunity among people.

## CLINICAL FEATURES (FIG. 1)

The disease has sudden onset. The incubation period is 2–12 days. The infection is characterized by fever, headache, fatigue, nausea, vomiting, muscle pain, rash and joint pain. Fever increases abruptly to as high as 103–104°F. It is accompanied by rigors. The acute phase lasts for 2–3 days.

### GENERAL FEATURES

- Febrile
- Dehydration
- Tender joint
- Swelling of the joint
- Maculopapular rashes

Joint pain is often severe in intensity. The arthralgia or arthritis is polyarticular, migrating. It predominantly affects small joints of hands,

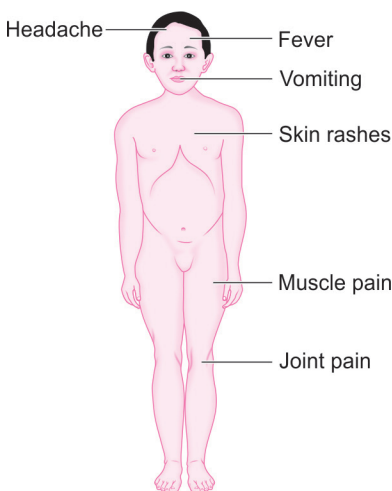


Fig. 1: Clinical features.

wrist, ankle and feet. There will be less involvement of large joints. Joint pain may continue for months after the illness. Headache is present in 80%. Photophobia and retro-orbital pain may also occur.

Maculopapular rashes are seen in 4–8 days later. This affects trunks and limbs. Inguinal lymph nodes may be enlarged. It is associated with young age.

### ESSENTIAL DIAGNOSTIC POINTS

- Outbreaks are seen in rainy season
- Fever, headache, fatigue
- Joint pain: Polyarticular, migrating
- Photophobia, retro-orbital pain
- Maculopapular rashes present in trunks and limbs
- Predominantly affects small joints, joint pain may continue for months

## DIAGNOSIS

It should be suspected in patients with characteristic triad of fever, rash and arthritis.

Virus may be isolated in cell cultures during the initial prodromal stage of 2–4 days. Polymerase chain reaction can be used to confirm the infection. Virus-related immunoglobulin M (IgM) antibodies may be detected by capture enzyme-linked immunosorbent assay (ELISA) and hemagglutination inhibition assays by 5–7 days of illness.

Some patients show leukopenia with mildly decreased platelet count. Elevated levels of aspartate aminotransferase (AST) and C-reactive protein (CRP) are also seen. However, virus isolation is the most definitive test in 1st week. Recently, reverse transcription polymerase chain reaction (RT-PCR) technique for diagnosis has been developed using nested primer pairs amplifying specific components of three structural gene regions. PCR results can be available within 1–2 days.

Serologic diagnosis can be made by demonstration of four-fold increase in antibody in acute and convalescent sera or demonstrating IgM antibodies specific for chikungunya virus (CHIKV). A commonly used test is the antibody capture ELISA (MAC-ELISA). Results of MAC-ELISA can be available within 2–3 days. Cross-reaction with other flavivirus antibodies such as O'nyongnyong and Semliki may occur in MAC-ELISA; however, the latter viruses are relatively rare in South East Asia. A positive virus culture supplemented with neutralization is taken as definitive proof for the presence of CHIKV.



Chikungunya should be suspected in patients who presents with the characteristic triad of fever, rash and arthritis. Viremia is present in most patients during the initial 2–4 days of disease and may be isolated in cell cultures. PCR can be used to confirm the infection. Virus specific IgM antibodies may be detected by capture ELISA and hemagglutination inhibition assays by 5–7 days of illness.

#### LABORATORY SALIENT FINDINGS

- Isolation of virus in cell culture
- Polymerase chain reaction
- IgM antibodies
- ELISA and hemagglutination inhibition assays

#### TREATMENT

No specific treatment is available. Symptomatic treatment includes rest, fluids and ibuprofen, naproxen, acetaminophen or paracetamol. This may relieve symptoms. Aspirin should be avoided during the acute phase.

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# Congenital Rubella

## PRESENTING COMPLAINTS

A newborn girl was brought with the complaint of rashes over the body 4–5 hours after the delivery.

### History of Presenting Complaints

A newborn girl was brought to attention of pediatrician for development of petechial rashes all over the body. The rashes appeared about 4–5 hours after the delivery.

She was the first sibling of consanguineous marriage. She was born at gestational age of 38 weeks. The delivery was normal. The baby cried immediately after the delivery. Features suggestive of intrauterine growth restriction (IUGR) were present. The birth weight was 1.7 kg.

Antenatal history revealed that the mother had mild fever at 12 weeks of amenorrhea. There was

associated history of rashes to the mother. This resolved with symptomatic management.

## EXAMINATION

Child was low birth weight baby with features of IUGR. Petechial rashes were present all over the body. Anthropometric measurement included, the length was 48 cm (10th centile), the weight was 1.7 kg (LBW), and the head circumference was 33 cm.

The child was afebrile. The pulse rate was 126 per minute, and the respiratory rate was 36 per minute. Blood pressure recorded was 50/40 mm Hg.

There was no pallor, no cyanosis and no icterus. Per abdomen examination revealed presence of hepatosplenomegaly. Eyes were small. There was absence of red reflex. Fundus could not be visualized probably because of the presence of the cataract in the right eye. In left eye, the fundus was clotted with fine deposits of the pigments, i.e., salt and pepper retinopathy.

### CASE AT A GLANCE

#### Basic Findings

Length	: 48 cm (10th centile)
Weight	: 1.7 kg [low birth weight (LBW)]
Temperature	: 37.5°C
Pulse rate	: 126 per minute
Respiratory rate	: 36 per minute
Blood pressure	: 50/40 mm Hg

#### Positive Findings

##### History

- Preterm delivery
- IUGR
- Rashes over the body
- Fever to the mother

##### Examination

- Petechial rashes
- Hepatosplenomegaly
- Cataract
- Salt-pepper retinopathy

##### Investigation

- TLC: Increased
- IgM level: Increased
- BT: Increased
- PT: Increased
- PTT: Increased

## INVESTIGATIONS

Hemoglobin	: 14.8 g/dL
TLC	: 11,000 cells/cu mm
ESR	: 24 mm in the 1st hour
HbSAg	: Negative
Platelet count	: 350,000 cells/cu mm
BT	: 7 minutes (Normal range: 3–5 minutes)
PT	: 25 seconds (Normal range: 11–15 seconds)
PTT	: 40 seconds (Normal range: 60–85 seconds)
LFT	: SGOT 45 U/L SGPT 30 U/L
Blood IgM	: Increased (normal <20 ng/dL)
Throat culture	: Negative

## DISCUSSION

A child presented with the rashes, i.e., petechial rashes after delivery with significant history of fever

in first trimester given the suspicion of TORCH [toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus (CMV), and herpes] infections. The associated features such as hepatosplenomegaly, salt and pepper fundal examination, cataract, thrombocytopenia make the diagnosis of congenital rubella syndrome.

Congenital infection produces a spectrum of illness known as the congenital rubella syndrome (CRS), a result of multiorgan, noninflammatory vasculitis triggered by persistent viral infection. Gregg, an Australian ophthalmologist, made the first link between rubella virus and fetal damage in 1941.

Congenital rubella is chronic infection, while acquired rubella is an acute infection. The fetus remains infected throughout gestation and for months and sometimes for years thereafter. The gestational age at which maternal infection occurs is a major determinant for the extent of fetal infection as well as the effects on the fetus.

Congenital rubella syndrome refers to infants born with defects secondary to intrauterine infection or who manifests symptoms or signs of intrauterine infection sometime after birth. Congenital infection is considered to have occurred if the infant has immunoglobulin M (IgM) rubella antibodies shortly after birth or if immunoglobulin G (IgG) antibodies persist for more than 6 months by which time maternally derived antibodies would have disappeared.

Rubella (German measles or 3-day measles) is a mild, often exanthematous disease of infants and children that is typically more severe and associated with more complications in adults. Its major clinical significance is transplacental infection and fetal damage as part of the CRS.

Rubella virus is a member of the family *Togaviridae* and is the only species of the genus *Rubivirus*. It is a single-stranded ribonucleic acid (RNA) virus with a lipid envelope and three structural proteins, including a nucleocapsid protein that is associated with the nucleus and two glycoproteins, E1 and E2 that are associated with the envelope.

## **PATHOGENESIS**

Rubella demonstrates a vascular endothelial cell tropism directed in large blood vessels at the inner layer of the vascular wall. At the cellular level, damage is linked to impaired replication, perturbation of cell growth, apoptosis, and postulated interaction between the viral nonstructural protein p90 and host cell regulatory proteins and timing of infection is of great importance.

Prospective studies after laboratory-confirmed rubella in pregnancy have documented that the rate of fetal infection is 90% after symptomatic maternal rubella during the first 12 gestational weeks; it drops to 25–30% during the second trimester and rises to 60–100% during the last weeks of gestation. During the second trimester, the fetus develops-increasing immunologic competence and no longer seems susceptible to the chronic infection characteristic of intrauterine rubella during the early weeks.

In general, earlier infection produces more extensive damage: Cardiac defects, cataracts, and glaucoma occur predominantly after maternal rubella during the first 2 months of pregnancy. Hearing loss and neurologic manifestations may occur any time during the first and, less commonly, into the second trimester. Late in pregnancy, infection does not appear to be teratogenic. Maternal infection with rubella during the first trimester of pregnancy frequently results in fetal infection following placental infection during maternal viremia.

Maternal viremia may lead to the seedling of the placenta. The placenta in turn may serve as a source of virus for the fetus. The gestational age of the conceptus at the time of the infection is critical factor in determining the outcome.

The viral mechanisms for cell injury and death in postnatal or congenital rubella are not well understood. Following infection, the virus replicates in the respiratory epithelium and then spreads to regional lymph nodes. Viremia ensues and is most intense from 10–17 days after infection. Viral shedding from the nasopharynx begins approximately 10 days after infection and may be detected up to 2 weeks following the onset of rash. The period of highest communicability is from 5 days before to 6 days after the appearance of the rash.

The most important risk factor for severe congenital defects is the stage of gestation at the time of infection. Maternal infection during the first 8 weeks of gestation results in the most severe and widespread defects. The risk for congenital defects has been estimated at 90% for maternal infection before 11 weeks of gestation. Defects occurring after 16 weeks of gestation are uncommon, even if fetal infection occurs.

The risk declines with each successive month of first trimester. However, growth retardation, deafness, microcephaly and mental retardation occur in infants infected during 4th month of gestation.

Rubella infection inhibits cell division and is probably reason of congenital malformation and

LBW babies. Necrosis of vascular endothelium is common and may lead to vascular obstruction with secondary damage to organs. Direct lysis of cells by rubella may occur particularly with myocardial, skeletal, muscle cells, and epithelial cells of lens.

If the infection is serious in the first trimester, spontaneous abortion and stillbirth may occur, or it may develop in multiple defects such as classical triad patent ductus arteriosus (PDA), cataract or deafness. Infection in the second trimester causes deafness. About 50–60% of fetuses are infected prior to 8th week of gestation and 10–20% of fetuses are infected during second trimester. Infection during third trimester is voluminous.

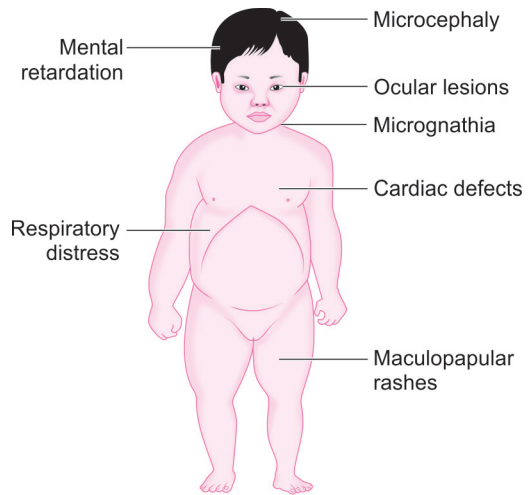
Causes of cellular and tissue damage in the infected fetus may include tissue necrosis due to vascular insufficiency, reduced cellular multiplication time, chromosomal breaks, and production of a protein inhibitor causing mitotic arrests in certain cell types. The most distinctive feature of congenital rubella is chronicity. Once the fetus is infected early in gestation, the virus persists in fetal tissue until well beyond delivery. Persistence suggests the possibility of ongoing tissue damage and reactivation, most notably in the brain.

Blueberry muffins are the skin lesions, hearing loss from the sensorineural deafness and meningoencephalitis. Persistent infection leads to pneumonia, hepatitis, bone lucencies, thrombocytopenia, purpura and anemia. Later sequelae include motor and mental retardation.

### CLINICAL FEATURES (FIG. 1)

The consequences of rubella in utero are varied and unpredictable. Spontaneous abortion, stillbirth, live birth with anomalies (single or multiple); and normal infants are represented in this spectrum. Virtually every organ may be involved, transiently or permanently, some with delayed onset.

During the newborn period, congenital rubella may be manifested by a number of acute conditions that are self-limiting in infants who survive. Neonatal thrombocytopenic purpura, characterized by a variable number of red purple macular, “blueberry muffin lesions”, is the most common and striking of these manifestations. It is usually associated with a high incidence of other transient lesions, such as radiolucencies in the metaphyseal portions of the long bones, hepatosplenomegaly, hepatitis, hemolytic anemia, and bulging anterior fontanelle with or without CSF pleocytosis. **Figures 2A to C** represent the most severe evidence of congenital infection. Low birth weight, cardiac defects, cataracts, deafness, and developmental



**Fig. 1:** Clinical features.

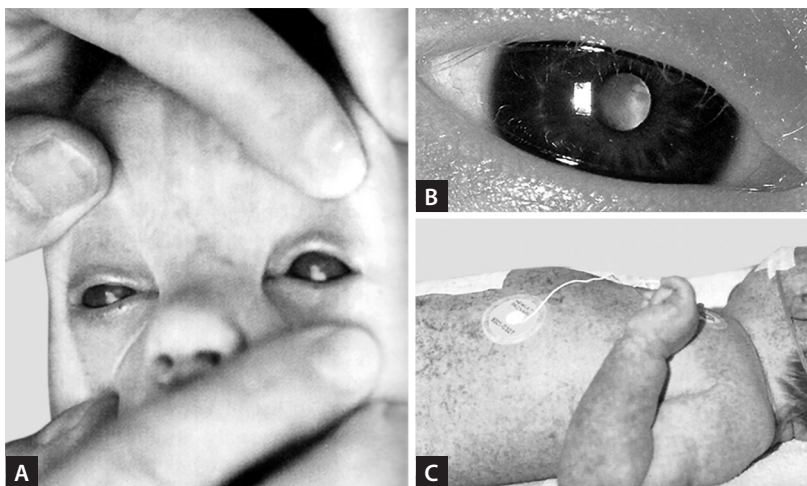
delay with or without microcephaly frequently accompany these transient lesions.

Signs of congenital heart disease such as cough, tachypnea and respiratory distress, LBW are commonly associated with congenital heart disease. Cardiac abnormalities occur in half of the children infected during the 1st 8 weeks of gestation. PDA is the most frequently reported cardiac defect, followed by lesions of the pulmonary arteries and valvular disease.

Patent ductus arteriosus, with or without stenosis of the pulmonary artery or its branches, and atrial and ventricular septal defects are the most common cardiac lesions encountered.

The most characteristic ocular anomaly is a pearly nuclear cataract, unilateral or bilateral, frequently associated with microphthalmia. The lesion may be absent at birth or so small that it may not be detected without careful ophthalmoscopic examination. Congenital glaucoma, which might be present at birth or which might develop during infancy, is clinically indistinguishable from hereditary infantile glaucoma. The cornea is enlarged and hazy, the anterior chamber is deep, and ocular tension is increased. Retinopathy, characterized by discrete, patchy black pigmentation, quite variable in size and location, is probably the most common ocular manifestation of congenital rubella. There is no evidence that this anomaly of the pigment epithelium of the retina interferes with vision.

Cataract is the most characteristic feature. Unilateral or bilateral cataracts are the most serious eye finding, occurring in about a third of infants. Ocular lesion may not be recognized until after the neonatal period. Retina may also be involved and



**Figs. 2A to C:** (A and B) Cataract; (C) Congenital rubella.  
(For color version see Plate 3)

lesion may be widespread, mottled with the black pigment deposits. These are variable in size and location—the salt and pepper retinitis.

Permanent sensorineural deafness caused by damage to the organ of Corti may be severe or mild and bilateral or unilateral. Defects in the middle ear structures have been reported. Deafness and communication disorders may be the only overt manifestations of congenital rubella, especially if maternal infection occurs after the first 8 weeks of pregnancy. Delayed psychomotor development during infancy is a hallmark of congenital rubella, with the most common consequence of the permanent brain damage being mental retardation, ranging from mild to profound.

Less common are severe spastic diplegia and autism. Progressive rubella panencephalitis, a severe progressive neurologic deterioration beginning during the second decade of life, is a rare complication of congenital rubella. Intellectual deterioration, myoclonus, ataxia, and seizures have progressed to death over the course of several years. High rubella antibody titers in serum and cerebrospinal fluid (CSF), elevated spinal fluid protein and gamma-globulin levels, histopathologic changes of progressive panencephalitis, and isolation of rubella virus from the brain biopsy specimen add to the obvious parallel between this condition and the subacute sclerosing panencephalitis that is a rare and late sequela of measles.

Neurologic abnormalities are common and may progress following birth. Meningoencephalitis is present in 10–20% of infants with CRS and may

persist for up to 12 months. Longitudinal follow-up through 9–12 years of infants without initial retardation revealed progressive development of additional sensory, motor, and behavioral abnormalities, including hearing loss and autism. Lethargy irritability, bulged AF and seizures may occur.

Congenital rubella syndrome also poses a risk of type 1 diabetes mellitus. By 10 years of age, the risk is at least 4 times greater in children with CRS than among healthy children, and by adult life, the risk is 10- to 20-fold greater. In one group of adult survivors, 40% had type 1 diabetes. The high prevalence of pancreatic islet cell cytotoxic or surface antibodies in congenital rubella patients with and without type 1 diabetes may reflect the in utero infection of pancreatic cells and play a role in the pathogenesis of type 1 diabetes in genetically susceptible individuals. Thyroiditis also has been described.

#### GENERAL FEATURES

- Sensory neural hearing defects
- Cardiac defects : PDA, VSD, PS
- Blood : Anemia  
Leukopenia  
Thrombocytopenia
- Ocular : Retinopathy  
Cataract  
Glaucoma
- Polycystic kidney

A variety of late-onset manifestations of CRS has been recognized. They include diabetes mellitus (20%), thyroid dysfunction (5%), and glaucoma and visual abnormalities associated



with the retinopathy, which had previously been considered benign.

#### ESSENTIAL DIAGNOSTIC POINTS

- Adenopathies, bone radiolucencies, encephalitis
- Cardiac defects: pulmonary arterial hypoplasia and patent ductus arteriosus
- Cataracts, retinopathy, growth retardation
- Hepatosplenomegaly thrombocytopenia and purpura
- Late sequelae include diabetes thyroid dysfunction, rubella encephalopathy, psychomotor problems

## DIAGNOSIS

The infant with suspected congenital rubella should be evaluated with specimens for viral detection and for rubella-specific IgM. These infants may remain chronically infected for many months after birth and thus are a source of infection for susceptible contacts for a year or more. Virus has been detected in pharyngeal secretions, blood spots, urine, CSF, cataract tissue, and virtually every organ. Reverse transcriptase polymerase chain reaction (PCR) using dried blood spots, lens aspirates, and oral fluids offers additional evidence for diagnosis in early infancy.

Newborn infants with congenital rubella have serum rubella antibody titers comparable to those of their mothers. Much of this antibody is transplacentally acquired IgG, but the presence of rubella-specific IgM reflects in utero antibody production by the fetus and, when present, is diagnostic of congenital rubella. In all but rare infants, by the end of 1 year, IgG is usually the dominant rubella antibody. Detectable levels of antibody persist for years in most children. Rubella antibody that persists in infancy beyond 6 months of age, without evidence of postnatal infection essentially confirms the diagnosis of congenital rubella.

Virus can be isolated from throat and urine from 1 week before to 2 weeks after the onset of rash. Congenital rubella is associated with low platelet counts, abnormal liver function tests, hemolytic pleocytosis and very high IgM antibody titer, X-ray shows pneumonitis, bone metaphyseal longitudinal lucencies in CRS.

#### LABORATORY SALIENT FINDINGS

- Leukopenia
- Low platelet count
- Abnormal liver function tests
- Hemolytic anemia, pleocytosis
- Very high rubella IgM antibody titers
- Serum IgM elevated
- Serum IgA and IgG levels may be depressed

## DIFFERENTIAL DIAGNOSIS

- TORCH
- Hepatitis
- Septicemia
- Encephalitis
- Hemolytic anemia
- Immune thrombocytopenia (ITP)
- Myocarditis.

## TREATMENT

There is no specific treatment. There is no specific antiviral medicine. Acetaminophen and ibuprofen are indicated for the fever.

Prevention is through immunization before puberty. After the puberty, immunization should be only after the estimation of hemagglutination inhibition (HI) antibody titer and if pregnancy can be avoided for 8 weeks.

If a pregnant mother is suspected to have exposed to possible rubella during early pregnancy (<16 weeks), HI antibody titer is estimated at 3 and 6 weeks intervals irrespective of occurrence of any rash. A four-fold or greater increase in HI antibody indicated rubella infection. If it is confirmed, medical termination is advised.

The immunization strategies to prevent congenital rubella infection have been modified.

- To protect the women of childhood bearing age (15–39 years)
- To prevent the transmission of rubella by vaccinating the children ages 1–14 years.

Only 30% of infants with encephalitis appear to escape residual neuromotor defects including autistic syndrome.

## Vaccination

Infants with CRS are contagious as long as they are shedding virus in their pharyngeal secretions. In general, infants who carry rubella for long periods are more severely damaged and delayed in growth and development. There is no specific therapy for congenital rubella. Early detection of auditory and visual impairment and incorporation of adequate educational therapy, including parent education and counseling, are important.

Ideally, postpubertal females should know their immune status before conception and be vaccinated only after assurance that they are not pregnant and can avoid pregnancy for at least 1 month after vaccination. Pregnant women should not be immunized but should be tested for rubella susceptibility. The immediate postpartum period is an excellent time to vaccinate

susceptible women, although barriers to post-partum or postabortal vaccination remain challenging. Vaccine virus has been isolated in human breast milk but poses no hazard to the infant. The use of  $\gamma$ -globulin (commercially available human immunoglobulin) in prophylaxis of rubella during pregnancy does not prevent rubella or congenital rubella in a predictable or reliable fashion.

Following a single dose of rubella RA 27/3 vaccine, 95% of persons, 12 months of age and older, develop serologic immunity, and after two doses, 99% have detectable antibody. Rubella RA 27/3 vaccine is highly protective as 97% of those vaccinated are protected from clinical disease after one dose. Detectable antibodies remain for 15 years in most individuals vaccinated following one dose, and 91–100% had antibodies after 12–15 years after two doses. Although antibody levels may wane, especially after one dose of vaccine, increased susceptibility to rubella disease does not occur.

Adverse reactions to rubella vaccination are uncommon in children. Measles, mumps, and rubella (MMR) administration is associated with fever in 5–15% of vaccinees and with rash in approximately 5% of vaccinees. Arthralgia and arthritis are more common following rubella vaccination in adults. Approximately, 25% of post-pubertal women experience arthralgia, and 10% experience arthritis. Peripheral neuropathies and transient thrombocytopenia may also occur.

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# Congenital Syphilis

## PRESENTING COMPLAINTS

A 2-month-old boy was brought with the complaints of:

- Swelling in the right leg since 15 days
- Excessive crying since 2–3 days

## History of Presenting Complaints

A 2-month-old boy was brought to the hospital with history of swelling in right leg. His mother complained that she noticed a small hard swelling at the lower end of leg. She also complained, the swelling was painful, his son was crying when it was touched. She also told that her child was crying excessively for 2–3 days. She found very difficult to console her child. Child used to cry a lot when he was being fed. There was also history of cough and cold. For the same, child had received a course of antibiotics.

## Past History of the Patient

The boy was the only child of nonconsanguineous marriage. The child was born at full term by normal

delivery. He cried immediately after the delivery. Cry of the baby was good. Birth weight of the child was 2.5 kg. The child was on breast milk after the delivery. There was no significant postnatal event. Child was discharged from the hospital on 3rd day.

## EXAMINATION

The boy was moderately built and nourished. He was crying excessively and was irritable. He was crying a lot when his limb was touched. Anthropometric measurements included, the length was 55 cm (25th centile), the weight was 4.5 kg (40th centile), and head circumference was 37 cm.

The child was afebrile, the heart rate was 126 per minute, and the respiratory rate was 24 per minute. Blood pressure recorded was 50/40 mm Hg. There was no pallor, swelling was present on both the lower limbs. There was no lymphadenopathy and no icterus. A small significant swelling was present on the right ankle joint. The swelling was firm in consistency. General signs of rhinitis were present. Other systemic examinations were normal.

## INVESTIGATIONS

Hemoglobin	: 12 g/dL
TLC	: 7,600 cells/cu mm
DLC	: $P_{77} L_{20} E_1 M_2$
ESR	: 30 mm in the 1st hour
AEC	: 440 cells/cu mm
Peripheral blood smear	: Microcytic hypochromic anemia
VDRL	: Positive

## DISCUSSION

It results from transplacental transfer of causative agent, *Treponema pallidum*. Clinical findings may be seen at birth or after several months. These include mucocutaneous manifestations. It is characterized by bullous rash. The denuded area is left after the rupture leading to crust formation. There will be pink to reddish maculopapular rash.

### CASE AT A GLANCE

#### Basic Findings

Length	: 55 cm (25th centile)
Weight	: 4.5 kg (40th centile)
Temperature	: 37°C
Pulse rate	: 126 per minute
Respiratory rate	: 24 per minute
Blood pressure	: 50/40 mm Hg

#### Positive Findings

##### History

- Excessive crying
- Swelling at the right leg
- Snuffles
- Cold
- Prior abortions

##### Examination

- Tender swelling
- Snuffles

##### Investigation

- VDRL: Positive
- Blood smear: Microcytic hypochromic anemia

Congenital syphilis results from the trans-placental infection of the developing fetus. An infected pregnant woman has a high probability of transmitting the infection to the fetus. Treponemal organisms can cross the placenta at any stage of pregnancy, but appear to elicit little tissue response before the 15th week of gestation. The rate of vertical transmission is 70–100% for primary syphilis, 40% for early-latent syphilis, and 10% for latent disease. Adequate treatment of the mother with penicillin protects the fetus, but the mother may become reinfected. The signs and symptoms are varied and may appear at any time between birth and 3 months of life, with 5 weeks as the median time of onset for those infants appearing normal at birth.

## CLINICAL FEATURES (FIG. 1)

### Early Congenital (Prenatal) Syphilis

Untreated syphilis in the pregnant woman can result in stillbirth, spontaneous abortion, nonimmune hydrops, premature delivery, perinatal death, and early or late congenital syphilis. Women with primary or secondary syphilis are more likely to have infants with adverse outcomes compared to women with early- or late-latent syphilis.

Most infants with congenital syphilis are asymptomatic at birth. Infants who develop clinical manifestations during the first 2 years of life are considered to have early congenital syphilis, whereas features that appears later, usually near puberty, compromise late congenital syphilis.

Clinical signs of congenital syphilis appear in approximately two-thirds of affected infants

during the 3rd to 8th week of life and in most by 3 months of age. Symptoms may be generalized and nonspecific (e.g., fever, lymphadenopathy, irritability, failure to thrive).

Alternatively, the highly suggestive triad of snuffles, palmar and plantar bullae and splenomegaly may be apparent. The severity of the clinical illness can vary from mild to fulminant, life-threatening disease. Premature infants are more likely to have hepatomegaly, respiratory distress and skin lesions than similarly infected term neonates.

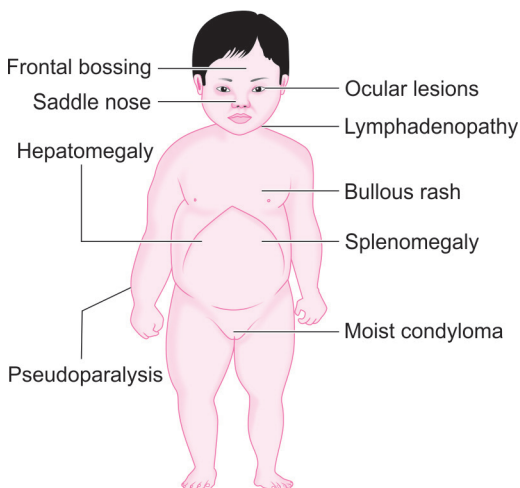
Rhinitis (i.e., snuffles) is encountered in 10–50% of infected infants and usually precedes the appearance of cutaneous eruptions by 1–2 weeks. The extremely contagious discharge initial is watery, but it later becomes thicker, purulent and even hemorrhagic. Without treatment, the nasal cartilage ulcerates with ensuing chondritis, necrosis and septal perforation (i.e., saddle-nose deformity of late congenital syphilis).

Most live-born syphilitic infants have no visible lesions at birth. When lesions are present, they are most commonly on the skin and in the bones. In the 1st week of life, syphilis may produce bullous lesions of the skin on the palms and soles. The more usual pattern of skin involvement is a diffuse, symmetric, copper-colored maculopapular rash that is most intense on the face, palms, and soles: It is an infiltrative lesion that when gently scraped with a scalpel yields serum teeming with treponemes. Thus, either dark-field microscopy or direct fluorescent antibody examination may result in a rapid and definitive diagnosis. If left untreated, most syphilitic infants will eventually have some kind of skin lesion.

A characteristic mucous membrane lesion of infants that has no counterpart in the adult is snuffles, a rhinitis producing a serous discharge that frequently becomes secondarily infected. Postinflammatory scarring beneath the nose is called rhagades. The lesion may extend to the nasal cartilage and cause sufficient damage to result in saddle nose deformity.

Rhagades are linear scars that extend in a spoke-like pattern from previous mucocutaneous fissure of the mouth. Rhagades are linear scars that radiate from sites of earlier mucocutaneous lesions of the mouth, nares and anus. Skeletal manifestations are caused by persistent or recurrent periostitis and its associated bone thickening. Throat involvement can produce hoarseness or aphonia.

The mucocutaneous lesions (**Fig. 2**) of congenital syphilis are varied and occur in 30–60%



**Fig. 1:** Clinical features.



**Fig. 2:** Mucocutaneous manifestation of an infant.  
(For color version see Plate 3)

of infants. The most characteristics are vesiculobullous eruptions that are more pronounced on the palms and soles. The commonly encountered rash consists of oval, red, maculopapular lesions that are most prominent on the buttocks, back, thighs and soles; they later change to a copper-brown color with superficial desquamation.

Other lesions may be annular, circinate, petechial or purpuric or have a blueberry muffin appearance. Mucous patches involving the nares, palate, tongue, lips and anus can occur; these lesions become deeply fissured and hemorrhagic and subsequently result in rhagades (i.e., parrot radial scars of late congenital syphilis).

Condyloma lata usually are encountered later in infancy in untreated patients. These raised, flat, moist and wart like lesions most commonly affect perioral (i.e., nares, angles of mouth) and perianal areas.

Congenital syphilis produces widespread lesions in the skeleton resulting in osteochondritis at metaphyseal plates, a generalized symmetric periosteal elevation, and symmetrically occurring osteomyelitic lesions on radiographs. The humerus is the most commonly involved bone, with the tibia next, which often has a highly characteristic pattern with a bilateral moth-eaten appearance; indeed, if other bones are involved these two bones are almost sure to be involved as well.

A bilateral moth-eaten appearance of the medial aspects of the proximal tibia that is highly characteristic of congenital syphilis has been described. More than 90% of infants with congenital syphilis manifest skeletal lesions that begin between 1 and 3 months of age; the process is

usually self-limited, with healing occurring spontaneously over the next few months, regardless of treatment.

Radiographic findings usually disappear by 5 months of age. The bone lesions are often asymptomatic. Occasionally, there is pain, often manifested by a pseudoparalysis that may be unilateral, involving either an arm or a leg (parrot paralysis). Later in infancy, there may be recurring isolated bone lesions; dactylitis, frequently asymmetric, is a typical example.

Central nervous system involvement with abnormal cerebrospinal fluid (CSF) findings is present in 40–60% of infants with syphilis. Jaundice as a manifestation of syphilitic hepatitis sometimes appears early in congenital syphilis and is resolved with treatment. Syphilitic pneumonitis, or pneumonia alba, is uncommon and usually is only present in fatal cases.

Splenomegaly and generalized lymphadenopathy is found in 20–50% of infants with congenital syphilis. The enlarged nodes are firm and nontender. These are frequent manifestations of the early systemic illness. The epitrochlear nodes commonly enlarge. Involvement of the kidney, when present, takes the form of a glomerulonephritis that presents as nephrotic syndrome. Syphilis is responsible for almost half of all nephrotic syndromes in patients <6 months of age.

Hepatosplenomegaly occurs in 50–90% of infants with early congenital syphilis. The enlargement is caused mainly by abundant extramedullary hematopoiesis and by subacute hepatic and splenic inflammation. Jaundice with direct and indirect hyperbilirubinemia, occurs in about one-third of infants and may be contributed to by hepatitis or hemolysis.

## Late Congenital Syphilis

Late congenital syphilis may be suspected from the stigmata, from the presence of continued active disease, or from persistently positive tests in an otherwise asymptomatic child. Hutchinson triad includes Hutchinson teeth, interstitial keratitis, and 8th nerve deafness. The most common stigmata are Hutchinson teeth, a screwdriver or peg-shaped deformity of the upper central incisors of the second dentition. Molars may have extra cusps and are referred to as “Mulberry molars.” They are poorly formed and crumble under normal use. All syphilitic teeth demonstrate deficient enamel and decay more readily than normal teeth. Hutchinson incisors are visible by radiography in its pre-eruptive site from about age year.



Interstitial keratitis begins between ages 5 and 16 years. The keratitis is an intense inflammatory vascular infiltration of the cornea that may be accompanied by an iritis, which may be followed by a dense cicatricial scar that produces blindness. Although usually bilateral, it may appear in one eye before it appears in the other eye. The lesion is not prevented by treatment given after the 1st year of disease. Early stages are characterized by marked photophobia, lacrimation, and a hazy appearance of the cornea. Later, scarring occurs.

Other active forms of the late disease are gummas and osteitis, which are among the late benign syphilitic lesions. The palate and nasal septum are predilectional sites for destructive gummas, with saddle nose and perforated palatal deformities possible end results. Saddle nose is the depression of the nasal root. Saddle-nose deformity, high arched palate and poor maxillary growth are late consequences of syphilitic rhinitis. It occurs as a result of syphilitic rhinitis that destroys the adjacent bone and cartilage. Perforated nasal septum is present.

Persistent periostitis gives rise to thickened clavicles and to a usually asymmetric saber shin. Clutton joints are symmetric synovial effusions, usually of the knees, that are sometimes painless, but which are more often warm and painful.

An important form of active late congenital syphilis involves the central nervous system (CNS), most commonly meningovascular. Paresis, a potentially more dangerous form of central nervous system syphilis, occurs in juveniles, and may be detected in a preparetic state by examination of CSF. The examination shows complement-fixing antibody, pleocytosis, and elevation of protein concentration. If untreated, parenchymal involvement may be severe and eventually irreversible. Juvenile tabes dorsalis rarely occurs.

Clinically silent CNS involvement occurs in as many as 60% of infants with congenital syphilis. Acute syphilitic meningitis may present with neck stiffness, vomiting, bulging anterior fontanelle and a positive Kernig's sign. CSF examination reveals a normal glucose concentration, modestly elevated protein content and mononuclear pleocytosis (usually <200 cells/mL) a pattern consistent with aseptic meningitis.

Chronic meningovascular syphilis develops in untreated infants and manifests in late infancy with progressive, communicating hydrocephalus, cranial nerve palsies, optic atrophy and cerebral infarctions leading to hemiplegia or seizure disorders.

### ESSENTIAL DIAGNOSTIC POINTS

- Fetal infection results in stillbirth premature infant
- Mucocutaneous lesions, lymphadenopathy
- Hepatosplenomegaly
- Bony changes, hydrops
- Hutchinson teeth and mulberry molars
- Keratitis, chorioretinitis glaucoma
- Hearing loss saddle nose
- Sabre shins, and mental retardation

Nephrosis and nephritis may be present at birth. Osteochondritis and syphilitic metaphysis occur within few months of life. Upper limbs are more often affected than lower limbs. The condition is generally unilateral. The long bones are painful. The infant may be unable to move the limb, i.e., pseudoparalysis. There may be acute syphilitic leptomeningitis, progressive hydrocephalus and cranial nerve palsies. Congenital glaucoma and chorioretinitis may also be seen.

### GENERAL FEATURES

- *Early:*
  - Bullous rash
  - Moist condyloma
  - Hepatosplenomegaly
  - Generalized lymphadenopathy
  - Hemolytic anemia
  - Nephrosis
  - Nephritis
  - Pseudoparalysis
  - Congenital glaucoma
  - Chorioretinitis
  - Failure to thrive
- *Late (after 2–3 years):*
  - Hutchinson's teeth
  - Frontal bossing
  - Saddle nose
  - High arched palate
  - Sabre tibia
  - Mulberry molars

## DIAGNOSIS

At birth, diagnosis of congenital syphilis is best established by demonstrating the spirochete or its deoxyribonucleic acid (DNA) in tissues or body fluids as previously alluded to. Serologic data obtained from cord blood or neonatal sera are helpful if interpreted with their limitations in mind.

If the infant's rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) titer is at least four fold higher than a concomitantly obtained maternal titer, the diagnosis of congenital syphilis is likely. The RPR may be negative in infants whose mother had acquired syphilis

shortly before delivery. The FTA-ABS-IgM test yields false positive and false negative results in 35 and 10% of cases respectively.

The diagnosis of congenital neurosyphilis is difficult to ascertain. CSF abnormalities such as mononuclear pleocytosis ( $\geq 25$  cells/mL), elevated protein concentration ( $>170$  mg/dL) and reactive CSF VDRL are widely used criteria. However, the CSF VDRL can be positive in the absence of neurosyphilis because of passive diffusion of non-treponemal IgG antibodies from serum to CSF and in infants with traumatic lumbar punctures.

The most useful tests in diagnosis and confirmation include VDRL and fluorescent treponemal antibody absorption tests. Positive serological tests in mother may be associated with possible test in newborn. Passively acquired VDRL from the mother resulting in positive test usually becomes negative within 3 months. A four-fold high titer of VDRL in the fetus as compared to mother is considered diagnostic.

Radiologic changes include osteochondritis, periostitis and osteitis. The earliest changes occur in the metaphysis and consist of transverse, serrated radiopaque bands (i.e., Wegner sign) alternating the zones of radiolucent osteoporotic bone. Osteochondritis becomes evident radiographically 5 weeks after fetal infection. The metaphysis may become fragmented. Periosteal reactions may consist of a single layer of new bone formation, multiple layers (onion peel periosteum) or a severe lamellar form (periostitis is radiologically apparent after at least 16 weeks) of fetal infection.

Hematologic abnormalities are common and include anemia, leukocytosis, leukopenia and thrombocytopenia. Anemia may be due to Coombs' negative hemolysis, replacement of bone marrow by syphilitic granulation tissue or maturation arrest in the erythroblastoid cell line. Thrombocytopenia is due to shortened peripheral platelet survival.

#### LABORATORY SALIENT FINDINGS

- VDRL test
- Fluorescent treponemal antibody absorption test
- CSF analysis: Mononuclear pleocytosis, elevated proteins, reactive CSF VDRL
- FTA-antibodies IgM test
- Demonstration of spirochetes or its DNA in tissue and body fluids

#### DIFFERENTIAL DIAGNOSIS

Differential diagnoses include cytomegalovirus (CMV) infection, toxoplasmosis, rubella and herpes simplex.

#### TREATMENT

The regimens of choice in proven or highly probable congenital syphilis in infants 4 weeks or younger are as follows:

- Aqueous crystalline penicillin G 100,000 to 150,000 IU/kg/day (administered as 50,000 U/kg intravenously every 12 hours during the first 7 days of life and every, 8 hours thereafter) for a total of 10 days; or
- Procaine penicillin G 50,000 U/kg intramuscularly daily in a single dose for 10 days; adequate CSF concentrations may not be achieved with this regimen.

The VDRL titers should be monitored every 2–3 months until they become nonreactive or the titer declines by at least four fold. Untreated infants should have FTA-ABS tests. Passively acquired maternal antibodies usually disappear by 6–12 months of age in uninfected infants.

The penicillin G treatment regimen for children  $>4$  weeks of age is 200,000–300,000 IU/kg/day administered as 50,000 IU/kg intravenously every 4–6 hours for 10 days. If 1 or more days of therapy are missed, the entire course needs to be restarted. Follow-up is particularly important for these infants. They should be seen frequently with a careful developmental evaluation, including vision and hearing testing. Nontreponemal tests should be repeated 3, 6, and 12 months after therapy. Titers are expected to decline and become nonreactive or stabilize at very low levels. In infants with congenital neurosyphilis or in those children not evaluated for neurosyphilis, the CSF should also be examined toward the end of therapy. Repeat treatment should be considered if the titer increases or fails to decrease four-fold within 1 year.

Infants with CSF abnormalities should be retested at 6 months of age. If the CSF VDRL is positive at that time, a second course of penicillin is indicated. Follow-up examinations should emphasize developmental assessment and a careful search for stigmata of congenital syphilis.

The following infants to be treated: (a) born to a mother who had untreated syphilis at delivery, (b) evidence of maternal relapse of reinfection, (c) physical evidence of active disease, (d) radiological evidence of syphilis, (e) reactive CSF VDRL.

If CSF is normal 100,000–150,000 IU of penicillin/kg/day in divided dose is given for 10–14 days. If the CSF is abnormal, the infant must be treated with 150,000 IU of penicillin per kg body weight per day in two divided doses are given IM or IV for minimum 21 days.

- *Interstitial keratitis*: Corticosteroids locally
- *Nerve deafness*: Oral steroids and penicillin
- Child should be kept under surveillance for 1 year
- Serological tests are repeated after 4–6 weeks.

## PREVENTION

Serologic tests for syphilis should be performed in all pregnant women prior to delivery and are required by law in many states. No infant should leave the hospital without the serologic status of the infant's mother having been documented at least once during pregnancy. Serologic testing also should be performed at delivery in communities and populations at risk for congenital syphilis. Serologic tests can be nonreactive among infants infected late during their mother's pregnancy. Penicillin is the only drug that, when given during

pregnancy, reliably protects the fetus. If other drugs such as erythromycin are used, the infant should be treated again after birth. The infected pregnant woman's sexual partners must also be treated because the mother could become reinfected and could also reinfect her infant after penicillin therapy. Because most open lesions and possibly blood are contagious, standard precautions are recommended for all patients with suspected or proven syphilis until therapy has been administered for at least 24 hours.

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# Dengue Fever

## PRESENTING COMPLAINTS

A 9-year-old boy was brought with the complaints of:

- Fever since 4 days
- Headache since 4 days
- Vomiting since 3 days
- Abdominal pain since 2 days
- Rashes since 2 days

## History of Presenting Complaints

A 9-year-old boy came to pediatric outpatient department with history of fever, headache, vomiting and abdominal pain. Mother told that his son had high fever associated with chills since

4 days. For which she took him to her family doctor and got the treatment. Boy was comfortable with treatment for 2–3 days. Later again he developed the fever. This time it was associated with severe headache not relieved with analgesic. Mother also gave history of vomiting about 3–4 times since yesterday. She even told that his son was not tolerating any food. Boy also told that he was having abdominal pain, especially in upper abdomen. Mother also revealed presence of some rashes over the body.

## Past History of the Patient

He was the elder sibling of nonconsanguineous marriage. He was born at full term with normal delivery. There were no significant postnatal events. He was on breastfeeds from the delivery and was exclusively on breast milk for 3 months. Later weaning was started and was on family food by 1 year. He was completely immunized. His developmental milestones were normal. His scholastic performance was normal. His sister was 5-year-old and was maintaining good health.

### CASE AT A GLANCE

#### Basic Findings

Height	: 128 cm (50th centile)
Weight	: 26 kg (75th centile)
Temperature	: 38°C
Heart rate	: 126 per minute
Respiratory rate	: 28 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- High degree fever
- Headache
- Vomiting
- Abdominal pain
- Rashes

##### Examination

- Toxic look
- Moderate dehydration
- Pallor
- Petechiae, ecchymosis
- Congested throat
- Tenderness in right hypochondrium
- Hepatomegaly
- Decreased breath sounds

##### Investigation

- Anemia
- Thrombocytopenia
- USG: Ascites
- Chest X-ray: Pleural effusion
- Tourniquet test: Positive

## EXAMINATION

Boy was moderately built and moderately nourished. Boy was looking sick and signs of moderate dehydration were present. He was in agony with pain in head and as well as in abdomen. The anthropometric measurement included, his weight was 26 kg (75th centile) the height was 128 cm (50th centile).

Boy was febrile. Signs of moderate dehydration were present. The heart rate was 126 per minute, respiratory rate was 28 per minute, and blood pressure was 70/50 mm Hg.

There was pallor, no lymphadenopathy, no edema and no clubbing. The petechiae and ecchymotic rashes were present over the face and legs. Throat was congested. Per abdomen examination revealed tenderness at the right hypochondrium, and epigastrium. Liver was palpable about 2–3 cm in the midclavicular line and tender.

Respiratory system revealed presence of decreased breath sounds on the right to basal region. Crepitations were present. Cardiovascular system was normal except for tachycardia. Central nervous system was normal. Tourniquet test was positive with the appearance of more rashes.

## INVESTIGATIONS

Hemoglobin	: 8 g/dL
TLC	: 14,200 cells/cu mm
DLC	: $P_{68} L_{28} E_2 M_2$
ESR	: 40 mm in 1st hour
Platelet count	: 35,000 cell/cu mm
PCV	: 60%
PT	: 12 seconds
SGPT	: 750 U/L (Normal range 6-50 U/L)
Chest X-ray	: Pleural effusion
Ultrasound abdomen	: Mild ascites hepatomegaly
Stool occult blood	: Positive

## DISCUSSION

Dengue fever, a benign syndrome caused by several arthropod viruses is characterized by biphasic fever, myalgia or arthralgia, rash, leukopenia and lymphadenopathy. Dengue hemorrhagic fever is an acute infectious thrombocytopenic purpura is a severe often fatal, febrile disease caused by dengue virus. It is characterized by capillary permeability, abnormalities of hemostasis and in severe cases, protein losing shock syndrome (dengue shock syndrome). It is currently thought to have an immunopathologic basis.

Dengue fever is a benign syndrome caused by several arthropod-borne viruses and is characterized by biphasic fever, myalgia or arthralgia, rash, leukopenia and lymphadenopathy. Dengue hemorrhagic fever is a severe, often fatal, febrile disease caused by 1 of 4 dengue viruses. It is characterized by capillary permeability, abnormalities of hemostasis, and, in severe cases, a protein-losing shock syndrome (dengue shock syndrome), which is thought to have an immunopathologic basis. It occurs when multiple types of dengue virus are simultaneously or sequentially transmitted. It occurs in endemic where warm temperature and practice of water storage in home, harboring permanent population of *Aedes aegypti*.

## PATHOGENESIS

There are at least 4 distinct antigenic types of dengue virus (dengue 1, 2, 3 and 4), members of

the family Flaviviridae. In addition, 3 other arthropod-borne viruses (arboviruses) cause similar or identical febrile diseases with rash.

Two main pathophysiological changes occur. There are increased vascular permeability that gives rise to loss of plasma from the vascular compartment leading to the hemoconcentration, low pulse pressure and other signs of shock. There is disorder in hemostasis involving the thrombocytopenia, vascular changes and coagulopathy. Platelet defects are both qualitative and quantitative. Maculopapular and petechial rashes are present.

There is evidence that non-neutralizing antibodies promote cellular infection and enhance severity of the disease. Dengue viruses demonstrate enhanced growth in cultures of human mononuclear phagocytes. There will be rapid activation of complement system. Shortly before the shock, blood levels of soluble tumor necrosis factor receptor interferon- $\gamma$  and interleukin-2 are elevated. These factors may interact at endothelial cell to produce increased vascular permeability through the nitric oxide final pathway.

The blood clotting and fibrinolytic systems are activated, and levels of factor XII are depressed. The mechanism of bleeding in dengue hemorrhagic fever is not known. But a mild degree of disseminated intravascular coagulation (DIC), liver damage and thrombocytopenia may operate synergistically. Capillary damage allows fluid, electrolytes, small proteins, red cells to lead into extravascular space. This result in hemoconcentration, hypovolemia, increased cardiac work, tissue hypoxia, metabolic acidosis and hyponatremia.

Early in the acute stage of secondary dengue infections, there is rapid activation of the complement system. Shortly before or during shock, blood levels of soluble tumor necrosis factor receptor, interferon- $\gamma$ , and interleukin-2 are elevated.  $Clq$ , C3, C4, C5-C8, and C3 proactivators are depressed, and C3 catabolic rates are elevated. These factors, the virus itself, or viral nonstructural protein 1 (NS1) may interact with endothelial cells, blood clotting factors, and platelets to produce increased vascular permeability. The blood clotting and fibrinolytic systems are activated, and levels of factor XII (Hageman factor) are depressed.

Usually deaths may be due to gastrointestinal or intracranial hemorrhage. Minimal to moderate hemorrhages are seen in upper gastrointestinal tract (GIT). Petechial hemorrhages are common



in interventricular septum of the heart. Focal hemorrhages are occasionally seen in lungs, liver, adrenals, and subarachnoid space. The liver is usually enlarged often with changes.

Microscopically there is perivascular edema in the soft tissues and widespread diapedesis of red cells. There may be maturational arrest of megakaryocytes in bone marrow and increased numbers of them are seen in capillaries of the lungs, in renal glomeruli, and in sinusoids of liver and spleen.

#### *Criteria for clinical diagnosis of dengue hemorrhagic fever (DHF)*

##### ■ *Clinical criteria:*

- Fever—acute onset, high continuous and lasting for 2–7 days
- Hemorrhagic manifestation—this includes at least positive tourniquet test. The standard method using the blood pressure cuff is recommended. In dengue hemorrhagic fever, the test usually gives the definite positive result, i.e., more than 20 petechiae per 2.5 cm<sup>2</sup>
- Enlargement of liver

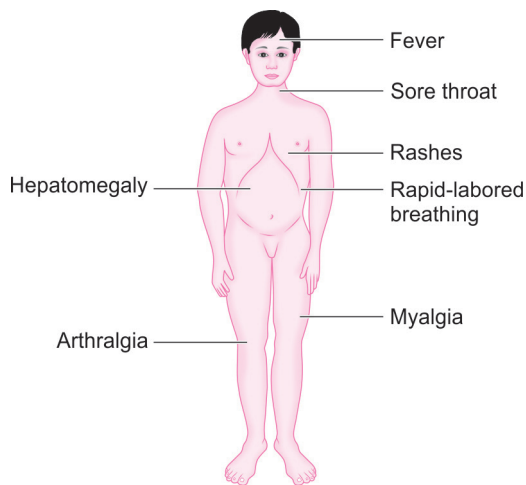
##### *Grading of severity of DHF*

- *Grade I:* Fever accompanied by nonspecific constitutional symptoms. The only hemorrhagic manifestation is positive tourniquet test.
- *Grade II:* Patient is characterized by spontaneous bleeding usually in the form of skin and other hemorrhagics in addition to the manifestation of grade I.
- *Grade III:* Circulatory failure characterized by rapid and weak pulse narrowing the pulse pressure (20 mm Hg or less) or hypertension with the presence of cold clammy skin and rashes.
- *Grade IV:* Profound shock and undetectable blood pressure and pulse.

In dengue shock syndrome, shock supervenes after a fever of 2–7 days. Skin becomes cool, bloated, congested, and pulse becomes rapid. Patient may be lethargic. There will be acute abdominal pain before the onset of shock. It is characterized by rapid, weak pulse with the narrowing of pulse pressure or hypotension. Untreated shock ends fatally in 12–24 hours. If shock is overcome, complete recovery occurs within 2–3 days.

## CLINICAL FEATURES (FIG. 1)

The incubation period is 1–7 days. The clinical manifestations are variable and are influenced



**Fig. 1:** Clinical features.

by the age of the patient. In infants and young children, the disease may be undifferentiated or characterized by fever for 1–5 days, pharyngeal inflammation, rhinitis, and mild cough. A majority of infected older children and adults experience sudden onset of fever, with temperature rapidly increasing to 39.4–41.1°C (103–106°F), usually accompanied by frontal or retro-orbital pain, particularly when pressure is applied to the eyes. Occasionally, severe back pain precedes the fever (back-break fever).

A transient, macular, generalized rash that blanches under pressure may be seen during the first 24–48 hours of fever. The pulse rate may be slow relative to the degree of fever. Myalgia and arthralgia occur soon after the onset of fevers and increase in severity over time. Joint symptoms may be particularly severe in patients with chikungunya infection. From the 2nd to 6th day of fever, nausea and vomiting are apt to occur, and generalized lymphadenopathy, cutaneous hyperesthesia or hyperalgesia, taste aberrations, and pronounced anorexia may develop.

Approximately, 1–2 days after defervescence, a generalized, morbilliform, maculopapular rash appears that spares the palms and soles. It disappears in 1–5 days, desquamation may occur. Rarely there is edema of the palms and soles. About the time this second rash appears, the body temperature, which has previously decreased to normal, may become slightly elevated and demonstrate the characteristic biphasic temperature pattern.

## Dengue Hemorrhagic Fever

Differentiation between dengue fever and dengue hemorrhagic fever is difficult early in the course of illness. A relatively mild first phase with abrupt onset of fever, malaise, vomiting, headache, anorexia and cough may be followed after 2–5 days by rapid clinical deterioration and collapse. In this second phase, the patient usually has cold, clammy extremities, a warm trunk, flushed face, diaphoresis, restlessness, irritability, midepigastric pain, and decreased urinary output.

Frequently, there are scattered petechiae on the forehead and extremities; spontaneous ecchymoses may appear, and easy bruising and bleeding at sites of venipuncture are common. A macular or maculopapular rash may appear, and there may be circumoral and peripheral cyanosis. Respirations are rapid and often labored. The pulse is weak, rapid, and thready and the heart sounds are faint. The liver may enlarge to 4–6 cm below the costal margin and is usually firm and somewhat tender.

Approximately, 20–30% of cases of DHF are complicated by shock (dengue shock syndrome). Dengue shock can be subtle, arising in patients who are fully alert, and is accompanied by increased peripheral vascular resistance and raised diastolic blood pressure. Shock is not from congestive heart failure but from venous pooling. With increasing cardiovascular compromise, diastolic pressure rises toward the systolic level and the pulse pressure narrows. Fewer than 10% of patients have gross ecchymosis or gastrointestinal bleeding, usually after a period of uncorrected shock. After a 24–36-hour period of crisis, convalescence is fairly rapid in the children who recover. The temperature may return to normal before or during the stage of shock. Bradycardia and ventricular extrasystoles are common during convalescence.

### GENERAL FEATURES

- Frontal and retro-orbital pain
- Severe back pain
- Transient macular generalized rash
- Relative bradycardia
- Petechial, maculopapular rash
- Circumoral and peripheral cyanosis
- Gastrointestinal bleeding

### Criteria for discharge:

- Afebrile at least 24 hours
- Passing urine normally
- Improved appetite
- No respiratory distress
- Stable hematocrit
- Platelet count more than 50,000/cu mm

### ESSENTIAL DIAGNOSTIC POINTS

- Fever, sore throat, retro-orbital headache
- Myalgia, arthralgia, petechial maculopapular rashes
- Hepatomegaly
- Gastrointestinal bleeding
- Thrombocytopenia
- DIC
- Low pulse pressure and circulatory failure
- Intracranial hemorrhage
- Respiratory distress

## DIAGNOSIS

The World Health Organization (WHO) criteria for dengue hemorrhagic fever are fever (2–7 days in duration or biphasic), minor or major hemorrhagic manifestations, thrombocytopenia (100,000/ $\mu$ L), and objective evidence of increased capillary permeability (hematocrit increased by 20%), pleural effusion or ascites (by chest radiography or ultrasonography), or hypoalbuminemia. Dengue shock syndrome criteria include those for dengue hemorrhagic fever as well as hypotension, tachycardia, narrow pulse pressure (<20 mm Hg), and signs of poor perfusion (cold extremities).

Virologic diagnosis can be established by serologic tests, by detection of viral proteins or viral RNA, or by the isolation of the virus from blood leukocytes or acute-phase serum. Following primary and secondary dengue infections, there is a relatively transient appearance of antidengue (immunoglobulin IgM) antibodies. These disappear after 6–12 weeks, a feature that can be used to time a dengue infection. In secondary dengue infections, most antibodies are of the IgG class.

Serologic diagnosis depends on a four-fold or greater increase in IgG antibody titer paired sera by hemagglutination inhibition, complement fixation, enzyme immunoassay, or neutralization test. Viral RNA can be detected in blood or tissues by specific complementary ribonucleic acid (RNA) probes or amplified first by polymerase chain reaction or by real-time polymerase chain reaction (PCR). A viral nonstructural protein, NS1, is released by infected cells into the circulation and can be detected in acute-stage blood samples using monoclonal or polyclonal antibodies. The detection of NS1 is the basis commercial tests, including rapid lateral flow tests. These tests offer reliable point of care diagnosis of acute dengue infection.

Pancytopenia may occur after 3–4 days of illness. Neutropenia may persist or may reappear. Hemoconcentration with an increase in hematocrit by 30% is present. There will be thrombocytopenia, prolonged bleeding time, and decreased

prothrombin level. There is moderate increase in transaminase level, raised BUN, and hypoalbuminemia. Neutropenia may persist or reappear during the latter stage of the disease and may continue into convalescence, with white blood cell counts  $<2,000/\text{mL}$ . Platelet counts rarely fall below  $100,000/\text{mL}$ . Venous clotting, bleeding and prothrombin times, and plasma fibrinogen values are within normal ranges. The tourniquet test result may be positive.

Mild acidosis, hemoconcentration, increased transaminase values, and hypoproteinemia may occur during some primary dengue virus infections. The electrocardiogram may show sinus bradycardia, ectopic ventricular foci flattened T waves, and prolongation of the P-R interval.

The most common hematologic abnormalities during dengue hemorrhagic fever and dengue shock syndrome are hemoconcentration with an increase of  $>20\%$  in hematocrit, thrombocytopenia, prolonged bleeding time, and a moderately decreased prothrombin level that is seldom  $<40\%$  of control. Fibrinogen levels may be subnormal, and fibrin split-product values are elevated.

Other abnormalities include moderate elevations of serum transaminase levels, consumption of complement, mild metabolic acidosis with hyponatremia, occasionally hypochloremia, slight elevation of serum urea nitrogen, and hypoalbuminemia.

Radiograph of the chest reveal pleural effusions (right  $>$  left) in nearly all patients with dengue shock syndrome. Ultrasonography can be used to detect serosal effusions of the thorax or abdomen. Thickening of gallbladder wall and presence of perivesicular fluid are characteristic signs of increased vascular permeability.

## Laboratory Diagnosis

- Thrombocytopenia
- Hemoconcentration-hematocrit is increased by 20% or more of the base true value.

The first two clinical criteria plus thrombocytopenia and hemoconcentration or a rising hematocrit are sufficient for the diagnosis.

### LABORATORY SALIENT FINDINGS

- Thrombocytopenia
- Hemoconcentration or raising hematocrit
- Serological tests
- Isolation of virus from blood leukocytes or serum
- Presence of anti-dengue immunoglobulin; IgM
- Pancytopenia
- Abdominal ultrasonography reveals ascites
- Chest X-ray shows pleural effusion

*Confirmation of diagnosis of dengue may be established by following:*

- Direct methods, including (a) virus isolation by culture; (b) genome detection by PCR; (c) NS1 antigen detection
- Indirect methods, including (a) IgM detection; and (b) IgG detection.

Virus isolation or PCR requires the sample to be obtained within the first 5 days of fever, is technically demanding, not universally available, expensive and hence of limited practical use. NS1 antigen is a highly conserved glycoprotein of dengue virus and secreted during the initial phase of illness. It disappears as the antibodies appear and hence declines as illness advances and in secondary dengue infections. The specificity is near 100% and sensitivity in the first 4 days of illness is 90% in primary dengue and 70% in secondary dengue infection.

Antibody determination needs careful interpretation. Following primary dengue infection, 80% of patients will have detectable IgM antibodies by day 5 and 99% by day 10. IgM antibodies peak by day 14 and are undetectable by 2–3 months. IgG antibodies rise later, peak to levels lower than IgM, decline slowly and remain detectable at low levels for life. Therefore, diagnosis of primary dengue infection is based on elevation of IgM.

## DIFFERENTIAL DIAGNOSIS

- Upper respiratory tract infection
- Influenza
- Malaria
- Yellow fever
- Leptospirosis
- Viral hepatitis

## COMPLICATIONS

- Dyselektrolytemia
- Hyperpyrexia
- Febrile convulsion
- Epistaxis
- Gastrointestinal bleeding

## TREATMENT

Treatment of uncomplicated dengue fever is supportive. Bed rest is advised during febrile period. Antipyretics should be used to keep the body temperature less than  $40^{\circ}\text{C}$ . Analgesic and mild radiation may be required. Fluid and electrolyte replacement required for the deficits caused by sweating, fasting, vomiting and diarrhea.

In case of dengue hemorrhagic fever, immediate evaluation of the vital signs and degree of hemoconcentration, dehydration and electrolyte imbalance should be done. Close monitoring is essential for at least 48 hours because shock may occur or recur. Patients who are cyanotic and labored breathing should be given oxygen. When elevation of hematocrit persists after the replacement of fluid, plasma or plasma colloids are indicated. Care must be taken to avoid overhydration. Fresh blood and platelet transfusion should not be given at the time of hemoconcentration.

Bed rest is advised. Antipyretic is advised. Aspirin is avoided because of gastritis, bleeding and acidosis.

Rise in hematocrit indicates significant plasma loss and need for the parenteral fluid therapy. For grade I and II—volume replacement should be done for 12–24 hours. The required fluid volume should be charted on 2–3 hours basis. The rate of administration is adjusted throughout for 24–48 hours. Serial hematocrit every 4–6 hours and frequent recording of vital signs should be done to avoid fluid overload.

*The types of fluid are:*

- Crystalloid—5% dextrose in RL  
5% dextrose in NS
- Colloids—Dextrose 40 and plasma

Paraldehyde may be required for children who are agitated. DIC should be managed accordingly. Hypovolemia during the fluid reabsorption phase may be life-threatening and is heralded by a fall in hematocrit with wide pulse presence. Diuretics and digitalization may be necessary.

Severe dengue should be hospitalized and treated with normal saline or ringer lactate; 10–20 mL/kg is infused over 1 hour or as bolus, if blood pressure is not recordable. In critically sick children, it is preferable to use two IV lines. One is for normal saline and other is for infusing 5% dextrose. If there is no improvement in vital parameters, PCV is rising, colloids 10 mL/kg are given rapidly. If PCV is falling without improvement in vital parameters, blood transfusion is indicated. When massive bleeding cannot be managed with fresh whole blood/fresh packed cells and there is possibility of DIC, combination of fresh frozen plasma and platelet concentrates should be considered.

Dengue shock syndrome indicates significant dehydration. Immediate rapid volume replacement is required. Rapid intravenous 10–20 mL/kg over 20 minutes is recommended. They may be

followed by another bolus. If hematocrit is rising plasma or 5% albumin (10–20 mL/kg) as rapid bolus in 20 minutes, is repeated if necessary.

If shock still persists, hematocrit is checked. Declining hematocrit suggests internal bleeding. Fresh whole blood 10 mL/kg is advised if hematocrit is >35%, concentrated platelet transfusion or fresh frozen plasma is indicated in cases of coagulopathy producing massive bleeding.

## Dengue Hemorrhagic Fever and Dengue Shock Syndrome

Dengue shock syndrome is a medical emergency that may occur in any child with a recent travel history to a tropical destination. Management begins with diagnostic suspicion and the understanding that shock often occurs during defervescence.

Management of dengue hemorrhagic fever and dengue shock syndrome includes immediate evaluation of vital signs and degrees of hemoconcentration, dehydration, and electrolyte imbalance. Close monitoring is essential for at least 48 hours, because shock may occur or recur precipitously early in the disease. Patients who are cyanotic or have labored breathing, should be given oxygen.

Rapid intravenous replacement of fluids and electrolytes can frequently sustain patients until spontaneous recovery occurs. Normal saline is more effective than the more expensive Ringer lactate saline in treating shock. When pulse pressure is more than 30 mm Hg or when elevation of the hematocrit persists after replacement of fluids, plasma or colloid preparations are indicated.

Transfusions of fresh blood or platelets suspended in plasma may be required to control bleeding; they should not be given during hemoconcentration but only after evaluation of hemoglobin or hematocrit values. Salicylates are contraindicated because of their effect on blood clotting.

## COMPLICATIONS

Fluid overload should be managed by oral furosemide 0.1–0.5 mg/kg/dose once or twice daily or continuous infusion of furosemide 0.1 mg/kg/h may be administered judiciously.

Hypervolemia during the fluid reabsorptive phase may be life threatening and is heralded by a decrease in hematocrit with wide pulse pressure. Diuretics and digitalization may be necessary.

Primary infections with dengue fever and dengue-like diseases are usually self-limited

and benign. Fluid and electrolyte losses, hyperpyrexia, and febrile convulsions are the most frequent complications in infants and young children. Epistaxis, petechiae, and purpuric lesions are uncommon but may occur at any stage. Blood from epistaxis that is swallowed, vomited, or passed by rectum may be erroneously interpreted as gastrointestinal bleeding. In adults and possibly in children, underlying conditions may lead to clinically significant bleeding. Convulsions may occur during high temperature, especially with chikungunya fever. Infrequently, after the febrile stage, prolonged asthenia, mental depression, bradycardia, and ventricular extrasystoles may occur in children.

## PROGNOSIS

### Dengue Fever

The prognosis is good. Care should be taken to avoid use of drugs that suppress platelet activity.

## Dengue Hemorrhagic Fever

The prognosis of dengue hemorrhagic fever is adversely affected by late diagnosis and delayed or improper treatment. Death has occurred in 40–50% of patients with shock, but with adequate intensive care, deaths should occur in <1% of cases. Infrequently, there is residual brain damage because of prolonged shock or occasionally of intracranial hemorrhage. Many fatalities are caused by overhydration.

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## PRESENTING COMPLAINTS

An 8-year-old boy was brought with the complaints of:

- Chest pain since 5 days
- Skin lesion since 2 days

## History of Presenting Complaints

An 8-year-old boy was brought to pediatric outpatient department with the history of onset of chest pain on the right side. The chest pain was not associated with any respiratory symptoms. It was not related to intake of food. Child had been taken to nearby clinic and he was prescribed some analgesics. But pain was not relieved. After 2 days, boy noticed some skin lesions at the site of chest pain. Skin lesion includes small vesicles. Itching was present along the lesion. Gradually the skin lesions increased in number along with one plane. Then again, he was taken to pediatric outpatient department, where it was diagnosed.

## Past History of the Patient

He was the first child of nonconsanguineous marriage. He was born at full term by normal delivery. There was no significant postnatal event.

He was on exclusive breast milk for 4 months. Later weaning was started and he was on family food by 18 months. His developmental milestones were normal. He had been completely immunized.

## EXAMINATION

On examination, boy looked very well built and nourished. He was in agony with pain. Anthropometric measurements included, the height was 130 cm (90th centile), and the weight was 26 kg (80th centile).

He was afebrile, the pulse rate was 96 per minute, and the respiratory rate was 20 per minute. Blood pressure recorded was 90/60 mm Hg. There was no pallor, no lymphadenopathy, no cyanosis and no edema. Small vesicular skin lesions were present at the infrascapular and inframammary region on the right side. Other systemic examinations were normal.

## INVESTIGATIONS

Hemoglobin	: 13 g/dL
TLC	: 7,600 cells/cu mm
ESR	: 22 mm in the 1st hour
X-ray chest	: Normal
Tzank preparation	: Showed multinucleated giant cells

## DISCUSSION (FIGS. 1A TO C)

The boy presented with vesicular skin lesion at the right infrascapular region and inframammary region along with the dermatome is characteristic of herpes zoster. It is caused by varicella zoster virus. The reaction occurs many months or years after the attack of chickenpox. It occurs in dorsal spinal or cranial nerve ganglion. This spreads to appropriate cutaneous dermatome.

Varicella-zoster virus (VZV) is one of the 9 human herpesviruses, which include herpes simplex virus (HSV) types 1 and 2 (**Fig. 2**), cytomegalovirus, Epstein-Barr virus, and human

### CASE AT A GLANCE

#### Basic Findings

Height	: 130 cm (90th centile)
Weight	: 26 kg (80th centile)
Temperature	: 37°C
Pulse rate	: 96 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 90/60 mm Hg

#### Positive Findings

##### History

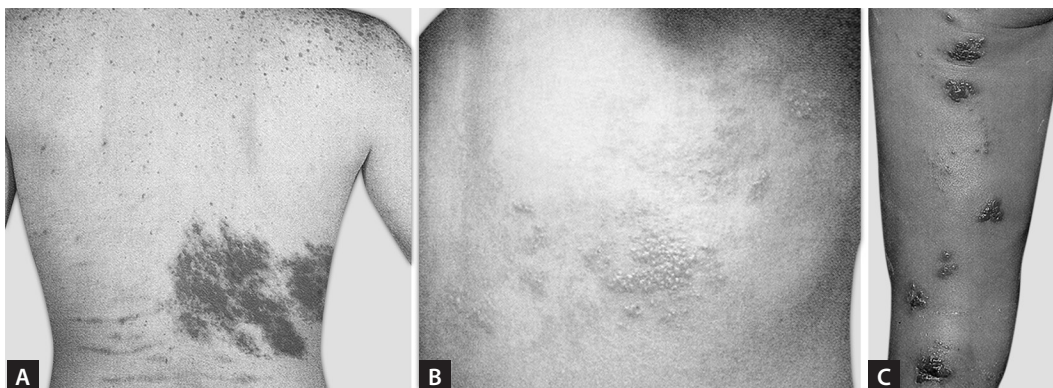
- Chest pain
- Vesicular lesion

##### Examination

- Vesicular lesion on the dermatome

##### Investigation

- Tzank preparation: Showed multinucleated giant cells



**Figs. 1A to C:** (A) Herpes zoster rash; (B) Vesicular rash; (C) S1 Dermatome.  
(For color version see Plate 3)



**Fig. 2:** Herpes simplex vesicles.  
(For color version see Plate 4)

herpesviruses 6A, 6B, 7, and 8. As with HSV-1 and HSV-2, VZV establishes latency in sensory or autonomic ganglia following primary infection, with the ability for subsequent reactivation.

The incidence of herpes zoster is highest in elderly individuals and in immunosuppressed patients. Spread from a contact with varicella is by respiratory secretions or fomites from vesicles or pustules, with a >95% infection rate in susceptible persons.

Varicella-zoster virus causes primary, latent, and recurrent infections. The primary infection is manifested as varicella (chickenpox) and results in establishment of a lifelong latent infection of sensory ganglion neurons. Reactivation of the latent infection causes herpes zoster (Shingles). Although often a mild illness of childhood, varicella can cause substantial morbidity and mortality in otherwise healthy children. Morbidity and mortality are higher in immunocompetent infants, adolescents,

and adults as well as in immunocompromised persons. Varicella predisposes to severe group A *Streptococcus* and *Staphylococcus aureus* infections. A clinically modified disease can occur among vaccinated persons (breakthrough varicella), usually with milder presentation. Varicella and herpes zoster can be treated with antiviral drugs.

## PATHOGENESIS

Humans are the only source of infection of VZV. Transmission occurs when aerosolized virus from skin lesions is exposed to the mucosa of the upper respiratory tract or conjunctivae of susceptible persons. Although it was long thought that the source of infection was the respiratory tract of infected individuals, very limited virus has been recovered from an infected person's airways and probably represents a much more limited source of infection than aerosolization from skin lesions.

The infectious period extends from up to 48 hours before the appearance of rash until all skin lesions are crusted over, usually about 5 days in normal hosts. Following infectious contact, the incubation period for varicella is 10–21 days and up to 28 days following a dose of varicella-zoster immunoglobulin (VariZIG).

Infection of cells within, the respiratory tract or conjunctivae by inhaled virions is followed by cell-associated spread to local lymph nodes, viremia, and then the development of the vesicular rash approximately 5 days later. Virus can be detected in circulating lymphocytes and monocytes. Cell-to-cell spread of virus, within the skin creates infected syncytia with a striking disruption of normal cellular architecture, and VZV-infected keratinocytes appear to elicit a vigorous type 1 interferon response in neighboring, uninfected cells

that restrains horizontal spread of virus and thus may contribute to the topology of the rash.

In the immunocompetent host, VZV viremia and the appearance of new skin lesions are curtailed within a few days by a vigorous cellular immune response comprising both natural killer (NK) and antigen-specific (T cell) components. Conversely, the failure to mount antigen-specific cellular responses is associated with progressive viral replication and dissemination and a potentially fatal outcome.

Individuals with disorders purely of humoral immunity do not suffer unusually severe or repeated episodes of varicella, indicating that cellular immunity affords sufficient protection against primary infection. However, a host humoral response is detectable within 4 days of the onset of the rash and can confer passive immunity; thus, pooled immunoglobulin derived from VZV-immune donors, known as VariZIG, can be used to protect VZV-exposed subjects at high risk of severe varicella. The presence of VZV-specific antibodies is also the best available correlate of protection against primary infection but is irrelevant to the risk of secondary (reactivation) disease.

Along with measles, varicella is one of the most highly communicable infections in humans, with household attack rates approaching 90%. In the absence of widespread vaccination, outbreaks of varicella occur readily within groups of susceptible children. In unvaccinated populations in temperate climates, seasonal peaks of varicella occur in the spring. These epidemics occur on a background of endemic disease, and 84% of children acquire infection by age 15 years. In contrast, the incidence of varicella in the tropics does not vary by season and tends to be delayed until adolescence or adult life.

Virus also reaches the ganglia by the hematogenous route and subsequent reactivation of latent virus causes herpes zoster, a vesicular rash that usually is dermatomal in distribution. During herpes zoster, necrotic changes may be produced in the neurons and surrounding satellite cells associated ganglia.

The skin lesions of varicella and herpes zoster have identical histopathology, and infectious VZV is present in both. Varicella elicits humoral and cell-mediated immunity that is highly protective against symptomatic reinfection. Suppression of cell-mediated immunity to VZV correlates with an increased risk for VZV reactivation as herpes zoster.

### CLINICAL FEATURES (FIG. 3)

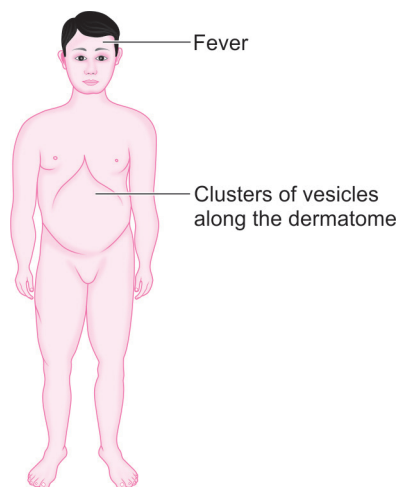
Exposure to varicella or herpes zoster has usually occurred 14–16 days previously (range 10–21 days). Contact may not have been recognized, since the index case is infectious 1–2 days before rash appears. Although varicella is the most distinctive childhood exanthema, inexperienced observers may mistake other diseases for varicella.

About 1–3 days prodrome of fever, respiratory symptoms and headache may occur, especially in older children. The pre-eruptive pain of herpes zoster may last several days and be mistaken for other illnesses.

Herpes zoster manifests as vesicular lesions clustered within one or, less commonly, two adjacent dermatomes. In the elderly, herpes zoster typically begins with burning pain followed by clusters of skin lesions in a dermatomal pattern.

The eruption of Shingles involves a single dermatome, usually truncal or cranial. The rash does not cross the midline. Ophthalmic zoster may be associated with corneal involvement. The closely grouped vesicles, which resemble a localized version of varicella or herpes simplex, often coalesce. The duration is 7–10 days before crusting.

Postherpetic neuralgia is rare in children. A few vesicles are occasionally seen outside the involved dermatome. Herpes zoster is a common problem in human immunodeficiency virus (HIV) infected or other immunocompromised children. Herpes zoster is also common in children who had varicella in early infancy or whose mothers had varicella during pregnancy.



**Fig. 3:** Clinical features.

Unlike herpes zoster in adults, zoster in children is infrequently associated with localized pain, hyperesthesia, pruritus, low-grade fever, or complications. In children, the rash is mild, with new lesions appearing for a few; symptoms of acute neuritis are minimal; and complete resolution usually occurs within 1–2 weeks. An increased risk for herpes zoster early in childhood has been described in children who acquire infection with VZV in utero or in the 1st year of life.

Immunocompromised children may have more severe herpes zoster, similar to the situation in adults, including postherpetic neuralgia. Immunocompromised patients may also experience disseminated cutaneous disease that mimics varicella, with or without initial dermatomal rash, as well as visceral dissemination with pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy.

Severely immunocompromised children, particularly those with advanced HIV infection, may have unusual, chronic, or relapsing cutaneous disease, retinitis, or central nervous system disease without rash. The finding of a lower risk for herpes zoster among vaccinated children with leukemia than in those who have had varicella suggested that the vaccine virus reactivates less commonly than wild-type VZV.

#### GENERAL FEATURES

- Fever
- Pruritus
- Hyperesthesia
- Neuritis

The history should exclude other cases of vesicular disease. Examination should include careful inspection of the number and character of the vesicles and also for the evidence of the complications such as bacterial superinfection, cutaneous dissemination, tenderness in the abdomen or liver. Fifth cranial nerve involvement produces the possibility of keratoconjunctivitis, uveitis or both.

#### ESSENTIAL DIAGNOSTIC POINTS

- History of varicella
- Local paresthesia and pain to eruption
- Dermatomal distribution of grouped vesicles on erythematous base
- *Distribution of rash:* 50% thoracic, 20% cervical, 20% lumbosacral, and 10% cranial nerve

## COMPLICATIONS

Complications of herpes zoster include secondary bacterial infection, motor or cranial nerve paralysis

(1 per 200 cases in adults), encephalitis, keratitis and dissemination in immunosuppressed patients. These complications are rare in immunocompetent children and they do not develop prolonged pain. Postherpetic neuralgia does occur in immunocompromised children.

## DIAGNOSIS

The diagnosis of VZV infection is usually made clinically. VZV is difficult to culture and requires fluid to be obtained from vesicles in the first few days of eruption. When successful, cytopathic effects in cell culture take many days. Detection of VZV DNA using a polymerase chain reaction (PCR) test currently is the diagnostic method of choice. This testing may be used to distinguish between wild-type and vaccine-strain VZV, using genotyping as well as to predict susceptibility to antiviral drugs.

During the acute phase of illness, the highest diagnostic yield is to test skin lesions by vesicular fluid aspiration or by swabbing or scraping the scab from crusted skin lesions. Early in the infection, VZV may be detected by PCR testing of saliva or buccal mucosal swabs. Tissue biopsy samples, blood, and cerebrospinal fluid also can be tested by PCR to confirm the diagnosis. Direct fluorescent antibody (DFA) assay can detect VZV using scrapings of a vesicle base in the first 3–4 days of the eruption and can provide a result quickly; however, the test is not as sensitive as PCR.

A number of sensitive serologic tests are available to measure antibodies to VZV. These include the fluorescent antibody to membrane antigen (FAMA) method, latex agglutination, and enzyme-linked immunosorbent assay (ELISA). Antibody to VZV develops within a few days after onset of varicella, persists for many years, and is present before the onset of zoster. VZV infections may be documented by a 2–4 fold rise in VZV antibody titer in acute and convalescent-phase serum specimens. Persistence of VZV antibody in infants beyond 8 months of age is highly suggestive of intrauterine varicella. Immunity to varicella is highly likely to be present if a positive titer of antibody (measured by a reliable assay) to VZV is demonstrated with a single serum sample from a child or an adult with no history of disease.

Leukocyte counts are normal or low. Leukocytosis suggests secondary bacterial infection. Multinucleated giant cells in a stained cytologic scraping from a vesicle base (Tzanck test) will indicate the presence of either a varicella-zoster virus or herpes simplex infection. Further distinction is usually made on clinical grounds.



**LABORATORY SALIENT FINDINGS**

- *Tzanck preparation*: Multinucleated giant cell
- Fluorescent antibody staining of lesion smear
- Serology
- Elevated serum aminotransferase

**DIFFERENTIAL DIAGNOSIS**

Herpes zoster is sometimes confused with a linear eruption of herpes simplex or a contact dermatitis.

- Atopic dermatitis
- Contact dermatitis
- Seborrheic dermatitis
- Impetigo contagiosa

**TREATMENT**

Treatment with antiviral therapy is dependent on host factors. Antiviral therapy is not recommended for otherwise healthy children with varicella if they are less than 12 years of age, although some would recommend the use of oral acyclovir or valacyclovir for the treatment of secondary household cases as they tend to experience more severe disease. In these children, benefit is only derived if therapy is started promptly as viral replication only occurs in the first 72 hours of illness.

Oral acyclovir or valacyclovir should be considered for persons considered at increased risk for severe varicella such as unvaccinated persons older than 12 years, people with chronic cutaneous or pulmonary disorders, people receiving long-term salicylate therapy, and people receiving short, intermittent, or inhaled courses of corticosteroids. Oral acyclovir or valacyclovir should be considered for pregnant women with varicella, with intravenous (IV) acyclovir being administered for more severe disease.

Acyclovir is used especially in immunocompromised person with increasing number of new vesicles, failure of vesicle maturation, abnormal liver function tests, onset of respiratory and CNS symptoms. The dose is 30 mg/kg/day in three divided doses for 7 days.

Antiviral drugs are effective for treatment of herpes zoster. In healthy adults, acyclovir (800 mg 5 times a day PO for 5–7 days), famciclovir (500 mg tid PO for 7 days), and valacyclovir (1,000 mg tid PO for 7 days) reduce the duration of the illness and the risk for development of postherpetic neuralgia. In otherwise healthy children, herpes

zoster is a less-severe disease, and postherpetic neuralgia usually does not occur. Therefore, treatment of uncomplicated herpes zoster in the child with an antiviral agent may not always be necessary, although some experts would treat with oral acyclovir (20 mg/kg/dose; maximum; 800 mg/dose) four times a day for 5 days, to shorten the duration of the illness. It is important to start antiviral therapy as soon as possible. Delay beyond 72 hours from onset of rash limits its effectiveness.

Intravenous acyclovir (10 mg/kg every 8 hours) therapy is recommended for all immunocompromised patients, including patients receiving high-dose corticosteroids for 14 days or more. Therapy should be initiated as soon as possible and should continue until no new lesions develop and all lesions have crusted over. Valacyclovir, which has improved oral bioavailability over oral acyclovir and has been shown to achieve serum levels comparable to IV acyclovir, can be considered in selected circumstances. IV acyclovir also is indicated for both term and preterm neonates who develop varicella from their mothers and should be considered for neonates who develop varicella following household exposure. Oral acyclovir is generally not indicated for treatment of young infants because of limited bioavailability and unreliable absorption in infants.

Wet to dry soaks are applied to the involved dermatome. Superficial infection is treated with penicillinase-resistant oral penicillin and topical antibiotics.

Analgesics are used to treat the pain. There is no indication for systemic steroids. Scopolamine eye drops are used to produce mydriasis and cycloplegia. Corticosteroid drops are indicated when interstitial keratitis or uveitis is present. Disseminated skin vesicles are seen.

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# Human Immunodeficiency Virus

## PRESENTING COMPLAINTS

A 3-month-old boy has brought with the history of:

- Not gaining weight since birth
- Loose motion since 2 months
- Cold, cough since 1 month

## History of Presenting Complaints

A 3-month-old boy was brought with the history of not gaining sufficient weight. Mother told that her son's birth weight was 3 kg. It has come down to 2.6 kg when she had checked 2 days back. The child was on exclusive breast milk. Mother also gave the history of loose motion 5–6 times a day since 2 months. She had shown to the nearby practitioner.

Mother also revealed the history of repeated attack of cold and cough for which she was showing to the doctor. As the child was not gaining weight, and because of repeated health problems, it was referred to hospital for the further management.

## Past History of the Patient

He is the first sibling of the consanguineous marriage. He has born at full term by vaginal normal delivery. He cried immediately after the delivery. Cry of the child was good. He was on breast feeds immediately after the delivery. His postnatal period was uneventful. He has received all basic immunization till date.

There was significant history of blood transition for the mother for the correction of hemoglobin in the antenatal period.

### CASE AT A GLANCE

#### Basic Findings

Length	: 53 cm (48th centile)
Weight	: 2.6 kg (40th centile)
Temperature	: 39°C
Pulse rate	: 120 per minute
Respiratory rate	: 28 per minute
Blood pressure	: 50/70 mm Hg

#### Positive Findings

- Not gaining weight
- Loose motion
- Cold and cough

#### Examination

- Poorly built
- Emaciated
- Febrile
- Tachypnea
- Cervical lymphadenopathy
- Hepatosplenomegaly
- Creptitation and rhonchi at lung

#### Investigation

Hemoglobin	: Decreased
ESR	: Raised
Chest X-ray	: Bronchopneumonia
USG	: Hepatosplenomegaly
CRP	: Positive
IgG	: Positive
Virology	: Positive

## EXAMINATION

On examination, the baby is poorly built and emaciated. There was loss of pad of fat over the buttocks. The anthropometric measurements included the height was 53 cm (48th centile), weight was 2.6 kg (40th centile). The head circumference was 36 cm.

Baby was febrile (39°C). The pulse rate 120 per minute and respiratory rate was 28 per minute. Mild costal retraction present. Signs of moderate dehydrate present. Blood pressure recorded was 50/70 mm Hg. Cervical lymphadenopathy was present. Per abdomen examination revealed the presence of the hepatosplenomegaly. Respiratory system revealed the presence of creptitation and rhonchi. Cardiovascular system was normal.

## INVESTIGATIONS

Hemoglobin	: 9.8 g/dL
TLC	: 2,800 cells/dL
DLC	: $P_{76} L_{20} M_2 E_2$
ESR	: 50 mm in the 1st hour
AEC	: 700 cells/cu mm
Chest X-ray	: Suggestive of bronchopneumonia

USG AG	: Hepatosplenomegaly
CRP	: Positive
IgG antibody	: Positive
Mantoux test	: Negative
Virology	:
HIV DNA	: Positive
HIV PCR	: Positive

## DISCUSSION

It has become an important cause of childhood morbidity and mortality especially in developing countries.

The human immunodeficiency virus (HIV)-1 and HIV-2 are members of Retroviridae family. They belong to lentivirus genus. HIV-1 genome has three major regions, Gag region, Pol region and Env region. The major external protein of HIV-1 is a heavily glycosylated gp120 protein. This contains the binding site for CD4 molecule. This is the most common T lymphocyte surface receptor for HIV. Most HIV strains have a specific tropism for one of the chemokines, fusion-inducing molecule, CXCR-4.

Conformational changes occur in gp120 and CD4 molecule following the viral attachment. This allows gp41 to interact with the fusion receptor on the cell surface. This results in the entry of viral ribonucleic acid (RNA) into the cell cytoplasm. Viral reverse transcriptase enzyme will transcribe the viral deoxyribonucleic acid (DNA) copies from the virus. RNA duplication of DNA produce durable stranded circular DNA. The circular DNA is transported into the cell nucleus. Here it is integrated into the chromosomal DNA. This is called as provirus. The proviruses can remain dominant for long period.

The HIV-1 transcription is followed by translation. This results in a capsid polypeptide. This is cleaved to produce the virus specific proteases. This is critical enzyme for HIV-1. The RNA genome is then incorporated into the newly formed viral capsid. As the new virus is formed, it buds through the cell membrane and is released.

The HIV-1 is transmitted via sexual contact, parental exposure to blood and or vertical transmission from mother to child. This primary route of infection in the pediatric population is vertical transmission.

Vertical transmission of HIV can occur during the intrauterine, intrapartum or through the breastfeeding. About 30% of infected newborns are infected in utero. The highest percentages of HIV, infected children require the virus intrapartum. Breastfeeding is an important route of transmission.

Transfusion of the infected blood or blood products have been accounted for all pediatric acquired immunodeficiency syndrome (AIDS) cases.

The risk factors for vertical transmission include preterm delivery (<34 weeks gestation) a low maternal antenatal CD4 count, >4 hours duration of ruptured membrane, and birth weight less than 2,500 g.

## PATHOGENESIS

If the intrauterine infection coincides with the period of rapid expansion of CD4 cells in the fetus. This could effectively infect the majority of the body's immunocompetent cells.

The mechanisms, by which HIV-infection causes this CD4<sup>+</sup> cell decline is not completely established, although possibilities include ongoing lytic infection, destruction of infected cells by host antiviral immune mechanisms, and death or dysfunction of lymphocyte precursors or accessory cells in the thymus and lymph nodes.

Once established, HIV-1 infection invariably persists. In the absence of ART, HIV continuously replicates and infects newly activated CD4<sup>+</sup> T lymphocytes. Ongoing generation of viral variants bearing escape mutations in immune epitopes contributes to evasion of host-neutralizing antibodies and cytotoxic T cells. Additionally, HIV-1 genomes integrate into the host chromosomal DNA to establish latent infection. Resting memory CD4<sup>+</sup> T lymphocytes appear to be the most important reservoir of latent HIV-1 infection. These cells stably harbor HIV-1 genomes even after years of viral suppression with ART, allowing viral rebound when ART is stopped. Early initiation of combination antiretroviral therapy (cART) may limit the extent of the latent viral reservoir.

In addition to CD4<sup>+</sup> T lymphocytes, other cells types such as tissue-resident macrophages can also be infected by HIV-1. These cells may also function as long-term viral reservoirs and contribute to organ-specific pathology, although some controversy remains. Even in individuals well controlled on cART, HIV-1 DNA may be recovered from brain, lung, liver, kidney, testes, and other tissues. HIV-1-related pathology involves many organs, although it is often difficult to know whether injury is primarily a consequence of local virus infection, immune-mediated cytotoxic effects, or associated infectious complications.

The majority of the prenatally infected newborn will show the much slower progression of disease with the median survival time of 6 years.

CD4 cell depletion may be less dramatic because infants normally have a relative lymphocytosis. Lymphopenia is relatively rare.

B-cell activation occurs in most children. This occurs early in infection as evidenced by hypergammaglobulinemia associated with the high levels of anti-HIV-1 antibody. This response may reflect both dysregulation of T-cell suppression of B-cell antibody synthesis and active CD4 enhancement of B lymphocyte humeral responses.

## CLINICAL FEATURES (FIG. 1)

The HIV-1 infection stage is determined by age-based CD4<sup>+</sup> T-cell count criteria. CD4<sup>+</sup> T-cell percentage is used for staging when absolute CD4<sup>+</sup> T-cell counts are not available. Patients with specific AIDS-defining clinical illnesses indicative of severe immunosuppression are classified as stage 3 regardless of CD4<sup>+</sup> T-cell count.

### Infant Infection

Perinatal HIV-1 infection is most often clinically silent at birth. In some instances, adenopathy may be detected in the 1st month of life. The incubation period, or interval before symptoms of HIV-1 infection become manifest, is generally shorter following perinatal infection than in adult HIV-1 infection. Viral load [determined by HIV-1 RNA polymerase chain reaction (PCR) quantification] in infants is typically high (>10 copies/mL) and often does not decline to a stable set point for several years. This protracted high-level viremia is likely due to immune immaturity, but it may also reflect

the high thymic output of CD4<sup>+</sup> T lymphocytes in early childhood that essentially provides fuel for viral replication.

Clinically silent abnormalities of immune function often precede HIV-1-related symptoms. Hypergammaglobulinemia with production of nonfunctional antibodies (polyclonal B-cell stimulation) is more common among HIV-1-infected infants than among adults, typically noted as early as 3–6 months of age. Despite the abundance of immunoglobulins, there is an inability to respond to new antigens with appropriate specific immunoglobulin production. This critically affects infants without prior antigen exposure, contributing to the greater frequency and severity of invasive bacterial infections seen in pediatric HIV-1 infection.

Frequencies of circulating CD4<sup>+</sup> T lymphocytes often drop by 1–2 months of age in vertically infected children, but CD4<sup>+</sup> depletion may not be readily apparent because of the higher baseline percentage and absolute numbers of lymphocytes in infants and young children than adults. The absolute CD4<sup>+</sup> count is not as predictive of the risk for opportunistic infections in infants as it is for older children and adults.

The first abnormalities detected include fever, failure to thrive, hepatosplenomegaly, generalized lymphadenopathy, parotitis, and diarrhea. Prior to the early use of cART, approximately 90% of perinatally HIV-1-infected infants would manifest 1 or more of these symptoms in the 1st year of life. In one study, the conditions that best discriminated between untreated HIV-1-infected and uninfected infants were chronic candidiasis, parotitis, persistent lymphadenopathy, and hepatosplenomegaly.

Approximately 20% of untreated HIV-1-infected infants present with rapidly progressive immune compromise and/or an AIDS-defining condition, such as *Pneumocystis jiroveci* pneumonia (PCP), or serious bacterial or fungal infections within the first 3–6 months of life. These infants have a high rate of mortality in the 1st year of life.

Beyond infancy, common symptoms of untreated HIV-1 infection in childhood include persistent adenopathy, hepatosplenomegaly, recurrent or chronic infections, growth failure, and developmental delay. With the exception of linear growth abnormalities, most of these symptoms are significantly less common and/or less severe with aggressive cART. With successful ART (good adherence and undetectable viral load), opportunistic infections are extremely rare. The development or worsening of HIV-1-related symptoms

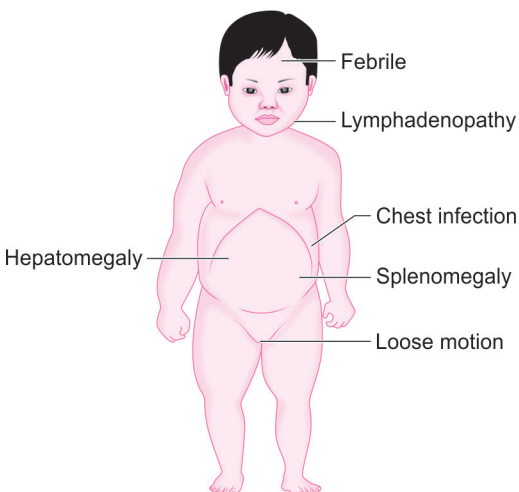


Fig. 1: Clinical features.

while receiving effective ART suggests clinical failure and possible resistance to one or more of the medications in the treatment regimen.

Central nervous system (CNS) is involved in more than 50% of infants infected perinatally. The most common presentation is progressively encephalopathy affecting the developmental milestones drastically. There will be cognitive deterioration, impaired brain growth resulting in acquired microcephaly and motor dysfunction. CNS infection can also occur.

GENERAL FEATURES

- Failure to thrive
- Cold and cough
- Nephritis
- Cardiac involvement
- Hepatitis
- CNS involvement

Childhood and Adult Infection

Hallmark stages of HIV-1 infection acquired in childhood or adulthood include an acute infection phase (seroconversion syndrome), often with flu-like symptoms and high-grade viremia; followed by period of immune containment of viral replication, during which the individual is usually free of symptoms; and a final period of progressive symptomatic immune compromise, with increasing viral replication.

During the asymptomatic phase, gradual and progressive abnormalities of immune function appear on testing. Viral load is usually lower than during the acute infection phase and may remain relatively stable at a set point for months to years.

The rapidity with which an infected adult or child progresses through the asymptomatic phase can be predicted to some degree by determining the individual's CD4<sup>+</sup> cell count and viral load. Lower CD4<sup>+</sup> cell counts and higher viral loads are each independent predictors, of more rapid disease progression.

The final phase, with symptomatic immune compromise, end-organ dysfunction, and HIV-associated malignancies, is correlated with increasing viral replication and often a change in viral tropism from use of cytokine receptor CCR5 to CXCR4, profound attrition of CD4<sup>+</sup> T lymphocytes, severe immune dysregulation (not just immune deficiency), and opportunistic infections.

Children with HIV infection with severe immunosuppression are susceptible to develop various kinds of infection. The important pathogens are *Pneumocystis jiroveci*, *Cryptosporidium*,

*Cryptococcus isospora* and cytomegalovirus (CMV). *Pneumocystis carinii* pneumonia is the opportunistic infection. The infection is more common between 3rd and 6th month of life. Recurrent bacterial infections produce recurrent pneumonia. The common pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*. Tuberculosis is an important infection associated with HIV. These infected children are likely to have extrapulmonary disseminated tuberculosis. The disease course is likely to be more rapid. The risk of tuberculosis is 5–10-fold higher in HIV patients.

Viral infections due to respiratory syncytial virus (RSV), influenza and parainfluenza virus results in asymptomatic disease. Adenovirus and measles produce more severe sequelae.

Fungal infections usually present as a part of disseminated disease in immunocompromised child. Pulmonary candidiasis should be suspected in any sick HIV infected child with lower respiratory tract infection.

A variety of microbes can cause gastrointestinal disease. These include *Salmonella*, *Campylobacter*, *Giardia*, CMV, rotavirus and *Candida*. AIDS enteropathy, a syndrome of malabsorption with partial villous atrophy not associated with specific pathogen. It is probably the result of direct HIV infectious of gut.

The inflammation of liver is caused by hepatitis by CMV, hepatitis B or C virus or mycobacteria.

Cardiovascular involvement are common persistent and often progressive. Left ventricular structure and function progressively may deteriorate in the first 3 years of life. This result is subsequent persistent mild LV dysfunction and increased LV mass in HIV infected children. ECG and echocardiogram are helpful in assessing cardiac function.

Nephritic syndrome is the most common manifestation. Polyuria, oliguria and hematuria have been observed.

ESSENTIAL DIAGNOSTIC POINTS

- Multiple serious bacterial infections
- Encephalopathy, recurrent *Salmonella* septicemia
- HIV wasting syndrome
- Disseminated fungal infection
- Mycobacterial infections
- Should have positive results for one or more of the HIV detection tests: HIV culture, HIV polymerase chain reaction (PCR), HIV antigen (p24)
- HIV-seropositive by repeatedly reactive enzyme immunosorbent assay and confirmatory test

## DIAGNOSIS

Early diagnosis of the infected infant is critically important, but early (prenatal) identification of the infant at risk for HIV-1 infection is equally vital. Only when HIV-1 infection in the pregnant woman is recognized is there an opportunity to implement strategies to prevent transmission and to screen exposed infants. HIV-1 screening and counseling should be a routine part of pregnancy care. Initial testing of the mother should be performed in the first trimester (or first visit later than first trimester) using current HIV-1/2 combination antibody/antigen assays. Repeat HIV testing in the third trimester (prior to 36 weeks of gestation) is recommended for pregnant women at increased risk for infection. Rapid HIV-1 antibody testing is advised for women who present to labor and delivery with unknown HIV status or ongoing high risk of infection.

The persistence of transplacentally acquired maternal antibody to HIV-1 in the infant complicates the use of conventional immunoglobulin G (IgG) antibody tests in diagnosing HIV-1 infection in infancy. Because such HIV-1 antibodies may remain in uninfected infants blood for up to 24 months, diagnosis of HIV-1 infection in the infant at risk requires the demonstration of HIV-1 nucleic acid in the peripheral blood by nucleic acid tests (NAT), namely HIV-1 DNA PCR or HIV-1 RNA PCR. Although the HIV-1 RNA PCR could be rendered falsely negative in an infected infant who is on antiretroviral prophylaxis, in practice, the current highly sensitive HIV-1 RNA PCR assays function as well as HIV-1 DNA PCR for screening vertically exposed infants. Serial virologic testing with either HIV-1 DNA PCR or HIV-1 RNA PCR can be expected to establish or exclude the diagnosis of HIV infection in an infant by 4 months of age.

Infants born to HIV-infected mother have antibody positive because of passive transfer of maternal HIV antibody across the placenta. A positive IgG antibody under the age of 18 months cannot be considered as diagnostic because of persistence of maternal antibodies. After the age of 18 months IgG antibody to HIV can be detected by reactive enzyme immunoassay (EIA) and confirmatory western blot test.

The optimal schedule for testing HIV-exposed infant includes HIV-1 NAT testing at 14–21 days, 4–6 weeks, and 4–6 months of age. Some experts also advice a test in the first 2–3 days after birth to identify infants who are viremic at birth from infection presumably acquired in utero. Because zidovudine monotherapy is used commonly in

HIV-1-exposed newborns, this early test can help avoid prolonged monotherapy, which could foster development of resistance. Presumptive noninfection with an HIV-1 can be determined with negative tests at >2 and >4 weeks of age (or 1 negative test at >8 weeks of age).

*Special tests:* Specific viral diagnostic assays such as HIV DNA or RNA PCR, HIV culture or HIV p24 antigen immune dissociated p24 (ICD-p24). These are essential for the diagnosis of young infants born to HIV infected mother. HIV DNA PCR is the preferred virologic assay in developed countries. The p24 antigen assay is less sensitive than the other virologic tests.

All infants born to HIV-infected mothers test antibody-positive at birth because of passive transfer of maternal HIV antibody across the placenta. Most uninfected infants lose maternal antibody between 6 and 12 months of age. As a small proportion of uninfected infants continue to have maternal HIV antibody in the blood up to 18 months of age, positive IgG antibody tests cannot be used to make a definitive diagnosis of HIV infection in infants younger than this age. In a child older than 18 months of age, demonstration of IgG antibody to HIV by a repeatedly reactive enzyme immunoassay (PIA) and confirmatory test (e.g., Western blot or immunofluorescence assay) can/establish the diagnosis of HIV infection.

Although serologic diagnostic tests were the most commonly used in the past, tests that allow for earlier definitive diagnosis in children have replaced antibody assays as the tests of choice for the diagnosis of HIV infection in infants.

Specific viral diagnostic assays, such as HIV DNA or RNA PCR, HIV culture, or HIV p24 antigen immune dissociated p24 (ICD-p24), are essential for diagnosis of young infants born to HIV infected mothers. By 6 months of age, the HIV culture and/or PCR identifies all infected infants, who are not having any continued exposure due to breast feeding. HIV DNA PCR is the preferred virologic assay in developed countries. Plasma HIV RNA assays may be more sensitive than DNA PCR for early diagnosis, but data are limited. HIV culture has similar sensitivity to HIV DNA PCR; however, it is more technically complex and expensive and results are often not available for 2–4 weeks compared to 2–3 days with PCR. The p24 antigen assay is less sensitive than the other virologic tests.

The national program (Early Infant Diagnosis) now uses HIV DNA PCR test on dried blood spot samples; the positive tests need confirmation using an HIV DNA PCR on a whole blood sample.



**LABORATORY SALIENT FINDINGS**

- Measurement of HIV antibody by ELISA
- *Confirmatory test:* Western blot
- HIV culture or, nucleic acid detection tests
- *Special tests:* HIV RNA and DNA at birth, PCR, HIV culture, or HIV p24 antigen immune dissociated p24(ICD-p24)

**TREATMENT**

Once a decision is made to treat, it should be expected that ART will continue for the remainder of the child's life. Factors to be considered in decisions about initiation of therapy include the risk of disease progression as determined by CD4<sup>+</sup> cell count and viral load, the potential benefits and risks of therapy, and the ability of the child and caregiver to adhere to administration of the therapeutic regimen. Issues associated with adherence should be fully assessed, discussed, and addressed with the child, if age-appropriate, and caregiver before the decision to initiate therapy is made.

Clinical and laboratory parameters need to be monitored carefully to detect any evidence of medication toxicity or treatment failure. ARI adverse events vary by medication, but some of the more common include neuropsychiatric symptoms (e.g., abnormal dreams, expression), gastrointestinal symptoms (e.g., nausea/vomiting, diarrhea), rash (rarely severe), lipodystrophy, low bone mineral density, dyslipidemia, hyperglycemia, hematologic abnormalities (e.g., anemia, neutropenia), lactic acidosis, nephrotoxicity, and hepatotoxicity.

To monitor for treatment failure, CD4<sup>+</sup> cell count and viral load should be monitored routinely every 3–4 months for at least the first 2 years of therapy. In children who are adherent to therapy, have CD4<sup>+</sup> cell counts well above the threshold for opportunistic infection risk, and have stable clinical status and viral suppression for more than 2 years, less frequent CD4<sup>+</sup> cell count monitoring (every 6–12 months) may be considered.

Effective treatment should result in maximal viral load reduction by 12–16 weeks after initiation of therapy. Virologic failure, defined as a repeated viral load >200 copies/mL after 6 months of therapy, suggests either a lack of adherence to the prescribed regimen or the presence or development of resistant virus.

Decisions concerning change in ART should be guided primarily by the child's prior medication history and antiretroviral resistance testing, including both past and current resistance test results. The initial antiretroviral regimen that a

child receives is the one most likely to achieve a sustained antiviral effect. In cases of virologic failure due to resistance, subsequent regimens are likely to be less effective because of the impact of cross-resistance to prior medications.

Clinical status at the time of initial presentation appears to correlate with prognosis in perinatally infected children. Perinatally HIV-1-infected infants appear to follow two basic patterns of disease progression. Approximately, 20% of perinatally infected infants progress rapidly and develop severe immune suppression and stage 3 disease in the 1st year of life if not treated appropriately. The majority of infants, however, have slower disease progression. Approximately 75% develop severe immune suppression by 6–10 years of age.

Assessment of the HIV-1-infected child should include a thorough physical examination and laboratory evaluation. To test for HIV-associated conditions (e.g., cytopenias, kidney disease, hepatitis) and to set the baseline for monitoring of antiretroviral toxicity, complete blood count with differential, comprehensive metabolic panel, urinalysis, and serum lipids should be measured in newly diagnosed children prior to initiation of ART.

Immunologic testing (CD4<sup>+</sup> cell count and quantitative immunoglobulins) will aid in decisions regarding PCP prophylaxis, intravenous immunoglobulin (IVIG) therapy, and initiation of ART. Quantitative HIV-1 RNA PCR (viral load) and antiretroviral drug-resistance testing should also be obtained at the time of diagnosis. Viral load and CD4<sup>+</sup> cell counts are independent predictors for risk of disease progression and should be monitored every 3–4 months whether or not the child is started on ART.

Clinical wellbeing in HIV-1-infected children can be estimated by assessment of growth rate (weight, length, and head circumference), developmental achievement, and experience with bacterial and viral infections. Following these clinical and laboratory parameters should assist in decisions concerning initiation and switching ART, prophylaxis for opportunistic infections, nutritional interventions, and psychosocial support efforts.

**Antiretroviral Therapy**

The currently available antiretroviral agents (ART) can be divided into five distinct categories: (1) nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), (2) non-nucleoside reverse

transcriptase inhibitors (NNRTIs), (3) protease inhibitors (PIs), (4) integrase strand transfer inhibitors (INSTIs), and (5) entry and fusion inhibitors.

For treatment of children, cART should usually be initiated with a combination of three drugs. The most effective regimens have included two NRTIs in combination with either an NNRTI, protease inhibitor, or INSTI. Considerations when choosing a regimen include patient age, results of antiretroviral resistance testing, barriers to adherence, drug toxicities, and differing drug formulations, among others.

Based on pediatric and adult studies of immediate versus deferred therapy, cART is recommended for all HIV-1-infected children regardless of clinical symptoms, immune status, or viral load, although the urgency and strength of the recommendation vary by age and level of immune suppression. Because approximately one-sixth of HIV-1-infected children experience rapid progression beginning in the 1st year of life, initiation of treatment is urgent in every child younger than 1 year as soon as the diagnosis is established.

Therapy is also considered urgent in children >1 year of age with an opportunistic illness (infection, HIV-associated malignancy, encephalopathy, or progressive multifocal leukoencephalopathy), as well as for children 1–5 years of age with CD4<sup>+</sup> cell count <500 cells/ $\mu$ L and children >6 years of age with CD4<sup>+</sup> cell count <200 cells/ $\mu$ L.

The national program for management of HIV-infected children recommends combination of zidovudine or abacavir + lamivudine + efavirenz as first line of therapy; for children <3 years of age, a protease inhibitor is used instead of NNRTI.

### Cotrimoxazole Therapy: HIV Exposed

It is recommended to all infants starting at 4–6 weeks of age and should be continued till HIV infection is excluded.

All children younger than 1 year of age documented to be living with HIV should receive cotrimoxazole prophylaxis regardless of symptoms or CD4 percentage.

After the age of 1 year, cotrimoxazole prophylaxis is recommended for symptomatic children.

All children who begin cotrimoxazole prophylaxis should continue until the age of 5 years, when they can be reassessed.

### Immunization

The vaccine as per the schedule should be administered to HIV-infected children. Symptomatic HIV-infected children should not be given OPV and BCG.

### Prevention of Mother to Child Transmission

These include antiviral prophylaxis to women during pregnancy and labor and to the infant in the 1st week of the life. Obstetric intervention includes elective cesarean delivery and complete avoidance of breastfeeding.

Treatment of pregnant women includes combination of zidovudine (AZC), lamivudine (3TC) and nevirapine (NVP). The recommended regimen for pregnant woman for preventing mother to child transmission is:

- *Antepartum*: AZT starting at 28 weeks of pregnancy
- *Intrapartum*: Combination of single dose of NVP, AZT and 3TC
- *Postpartum*: Combination of AZT and 3TC for 7 days

Antiretroviral therapy for infants born to HIV positive mother include single dose of NVP and AZT for 1 week. When the delivery occurs within 2 hours of a woman taking single dose NVP, the infant should receive single dose NVP immediately after the delivery and AZT for 4 weeks.

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# Infectious Mononucleosis

## PRESENTING COMPLAINTS

A 3-year-old girl was brought with the complaints of:

- Fever since 1 week
- Throat pain since 5 days
- Rashes since 3 days

## History of Presenting Complaints

A 3-year-old girl was brought to the pediatric outpatient department with the history of fever, throat pain and rashes over the body. According to the mother, fever was of moderate to high degree, intermittent type, not associated with chills and rigors. Fever used to reduce with paracetamol. Mother also told that her daughter was complaining of the throat pain, difficulty in swallowing the food, associated with occasional vomiting. Mother had noticed the maculopapular rashes over the body,

which were itching. She also revealed the appetite of her daughter has come down drastically. There was no loose motion, no cough and cold.

## Past History of the Patient

She was the only sibling of nonconsanguineous marriage. She was born at full term by normal delivery. Her birth weight was 3 kg. She started taking breast milk immediately after delivery. There was no significant postnatal event. Weaning was started in the 4th month and completed by 1 year. She was immunized completely and all the developmental milestones were normal.

## EXAMINATION

The girl was moderately built and nourished. She was looking tired and dehydrated. She was carried by her mother. She was irritable and not allowing to examine. Anthropometric measurements included the height 95 cm (75th centile), weight was 13 kg (50th centile). There were signs of moderate dehydration.

The child was febrile 39°C. The pulse rate was 124 per minute. The respiratory rate was 22 per minute. Blood pressure recorded was 70/50 mm Hg. There was no pallor. There was generalized lymphadenopathy involving cervical group. There was no cyanosis and no clubbing. There were maculopapular rashes present over the body.

Per abdomen revealed the presence of hepatomegaly. Liver was palpable 2 cm below the costal margin, nontender. Throat congestion was present. Bowel sounds were normal. Cardiovascular and respiratory system was normal.

## INVESTIGATIONS

Hemoglobin	: 11 g/dL
TLC	: 12,000 cells/cu mm
DLC	: P <sub>68</sub> L <sub>28</sub> E <sub>2</sub> M <sub>2</sub>
ESR	: 30 mm in the 1st hour
LFT	: SGOT—increased SGPT—increased

### CASE AT A GLANCE

#### Basic Findings

Height	: 95 cm (75th centile)
Weight	: 13 kg (50th centile)
Temperature	: 39°C
Pulse rate	: 124 per minute
Respiratory rate	: 22 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Fever
- Throat pain
- Maculopapular rashes

##### Examination

- Febrile
- Lymphadenopathy
- Dehydration
- Hepatomegaly

##### Investigation

- SGOT: Increased
- SGPT: Raised
- Paul Bunnell test is positive
- USG: Hepatomegaly

Paul Bunnell test : Positive  
Chest X-ray : NAD  
Ultrasound  
abdomen : Hepatomegaly is present

## DISCUSSION

Child has presented with the history of fever, throat pain and also maculopapular rashes. This along with lymphadenopathy and hepatomegaly associated with abnormal liver function test and positive Paul-Bunnell test indicates the infectious mononucleosis.

Epstein-Barr virus (EBV) was implicated as the etiological agent for infectious mononucleosis. Most of the cases are observed in older children but no age is exempted. EBV infections are much more common in pediatric population than commonly believed, for they are mostly subclinical.

Epstein-Barr virus is recognized as the major cause of infectious mononucleosis (IM). Most EBV infections are thought to be spread through saliva. Manifestations of EBV infection are varied and range from asymptomatic infection to fulminant lymphoproliferative disease. EBV is also associated with a number of malignancies, including endemic Burkitt lymphoma, nasopharyngeal carcinoma, Hodgkin disease, and a spectrum of post-transplant lymphoproliferative disease.

Mononucleosis is the most characteristic syndrome produced by EBV infection. Young children infected with EBV have either no symptoms or a mild nonspecific febrile illness. As the age of the host increases, EBV infections are more likely to produce the typical features of the mononucleosis syndrome in 20–25% of infected adolescents. EBV is acquired readily from asymptomatic carriers (15–20% of whom excrete the virus on any given day) and from recently ill patients, who excrete virus for many months. Young children are infected from the saliva of playmates and family members. Adolescents may be infected through sexual activity. EBV can also be transmitted by blood transfusion and organ transplantation.

Transmission occurs by intimate contact between susceptible individual and asymptomatic shedders of EBV. Blood transfusion is another possible way of transmission.

## PATHOGENESIS

Epstein-Barr virus is a member of the family Herpesviridae (gamma herpesvirus), which contains linear double-stranded deoxyribonucleic acid (DNA) surrounded by a protein capsid. EBV causes

lytic infection of human oropharyngeal and salivary cells and latent infection of human and primate B lymphocytes as well as epithelium of the nasopharynx. It has long been recognized to be lymphotropic for B lymphocytes and to infect both oropharyngeal epithelial cells and myocytes, but it is also true that it infects T lymphocytes and natural killer cells.

Infection of lymphocytes with linear EBV DNA can transform them into continuously growing lymphoblastoid cell lines containing a circular DNA episome. Once infected, transformed lymphoblastoid cells rarely continue to produce infectious virus in vitro, although EB antigens can be detected in the cells. The appearance of new antigens on the cell surface of EBV-infected cells is believed to be responsible for the cellular immune response to the virus and for pathogenesis of the resulting disease. The EBV receptor on epithelial cells and B lymphocytes is the CD21 molecule (formerly CR2), which is also the receptor for the C3d fragment of the third component of complement. The virus elicits both humoral and cellular immune responses.

Epstein-Barr virus acquired by ingestion appears to first infect either oropharyngeal resting B cells or epithelial cells and then B cells. Subsequently the virus infects other susceptible B lymphocytes within the lymphoid tissue of the pharynx. During a 30- to 50-day incubation period, virus actively replicates and disseminates throughout the entire lymphoreticular system.

Epstein-Barr virus is excreted in oropharyngeal secretions and is transmitted by contact with saliva via kissing or other mucosal contact with contaminated objects. Healthy seropositive individuals intermittently shed EBV in their oropharynx. Mucosal contact with the saliva of these individuals is the likely mechanism of infection in preadolescent and adolescent individuals.

Epstein-Barr virus (a DNA virus of herpesvirus group) infects susceptible B lymphocytes by attaching to its specific C3d receptor on cell surface where it undergoes multiplication. Later, it disseminates throughout the lymphoreticular system. The virus elicits both humoral and cell mediated immunity. The antibodies are produced against the EBV virus.

The cell-mediated immunity is provided by the T lymphocytes which proliferates extensively in response to B-lymphocyte infection. In the peripheral blood, this is reflected by the appearance of many atypical T lymphocytes.

These cytotoxic/suppressor cells prevent the proliferation of EBV infected lymphoid cells. Children with defect in their cell-mediated immunity are prone to develop fatal disease or lymphoproliferative disorder including B-cell lymphomas.

CLINICAL FEATURES (FIG. 1)

The incubation period of EBV-IM is 30–50 days. The clinical syndrome of EBV-IM is usually preceded by a 5-day prodrome of malaise, fatigue, headache, nausea, abdominal pain, or some combination of these symptoms. Over the next 7–20 days, sore throat and fever gradually increase.

The triad of fever, sore throat, and posterior cervical adenopathy occurs in more than 80% of symptomatic patients. Sore throat is often accompanied by evidence of moderate-to-severe pharyngitis, with marked tonsillar enlargement that may be covered with shaggy gray or white exudate.

Fever is present in 85–95% of patients, from 39°C (102°F) up to 40.5°C (105°F), and on average lasts 10 days but may persist for weeks. Fatigue and lymphadenopathy may persist longer.

Adenopathy most often involves only the bilateral posterior cervical nodes but may involve any node, including anterior cervical, epitrochlear, or even generalized lymph nodes. Nodes may be affected singly or in groups (not necessarily symmetrical) and may be very large or small. They are most often firm, discrete, and moderately tender to palpation.

In most cases a maculopapular rash develops. Patients have a rash, which can be macular, scarlatiniform, or urticarial. Rash is almost universal in patients taking penicillin or ampicillin. Soft palate petechiae and eyelid edema are also observed.

Massive splenomegaly may occur, usually defined operationally as a spleen extending well into the left lower quadrant or pelvis or that has crossed the midline of the abdomen and that weighs at least 500–1,000 g. Rupture is rare but can be a potentially fatal complication. Hepatomegaly occurs.

Serum aspartate aminotransferase (AST) and serum lactate dehydrogenase (LDH) are mildly elevated in the majority of patients and may persist for weeks to months. Chronic liver disease, however, does not typically result.

Other clinical findings include bilateral supraorbital edema and rashes. A blanching, erythematous, maculopapular exanthema occurs in about 59–15% of patients, but as many as 80% develop this rash if treated with ampicillin or other  $\beta$ -lactam antibiotics. The same rash may occur with cytomegalovirus (CMV)-associated mononucleosis and so does not differentiate CMV from EBV-associated mononucleosis. Urticarial, bullous, hemorrhagic, and scarlatiniform rashes, as well as the Gianotti-Crosti syndrome, are also associated with IM.

Neurologic complications include aseptic meningitis, encephalitis optic neuritis, Guillain-Barré syndrome, transverse myelitis, Bell palsy, and, in numerous more recent epidemiologic studies, multiple: sclerosis following EBV-IM.

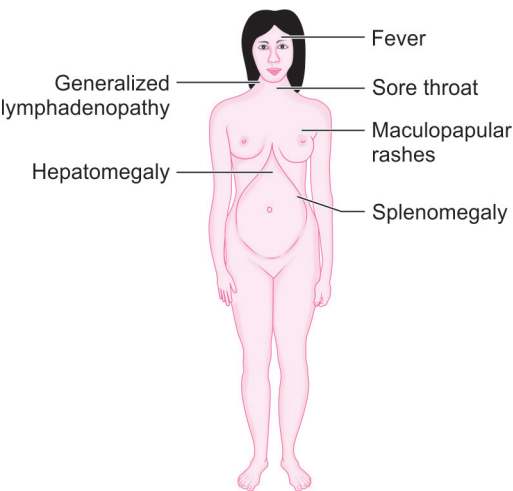


Fig. 1: Clinical features.

GENERAL FEATURES
<ul style="list-style-type: none"><li>• Malaise</li><li>• Loss of appetite</li><li>• Periorbital edema</li></ul>

There may be ulceration in oral cavity with enanthems at junction of hard and soft palate. Spleen is enlarged in more than half of the patients. Periorbital edema is reported in 33% patients. Hepatomegaly is common (30%), and the liver is frequently tender.

COMPLICATIONS

- *Respiratory:* Pneumonia, severe airway obstruction
- *Neurologica:* Convulsions, aseptic meningitis, transverse myelitis and Guillain-Barré syndrome



- **Hematological:** Immune hemolytic anemia of cold antibody type, thrombocytopenia, aplastic anemia and hemorrhage
- **Splenic rupture:** Rupture of rapidly enlarging spleen may follow minor trauma
- **Others:** Myocarditis, hepatitis, glomerulonephritis, orchitis, etc.

#### ESSENTIAL DIAGNOSTIC POINTS

- Prolonged fever
- Exudative pharyngitis
- Generalized lymphadenopathy
- Hepatosplenomegaly
- Heterophile antibodies
- Atypical lymphocytes

### LABORATORY INVESTIGATIONS

- **Peripheral blood:** Leukopenia may occur early, but an atypical lymphocytosis is most notable. Hematologic changes may not be seen until the 3rd week of illness and may be entirely absent in some EBV syndromes. There is usually an absolute increase in the lymphocytes in the peripheral blood. Most lymphocytes are large and atypical, with pale blue vacuolated cytoplasm and an eccentric nucleus. SGOT and SGPT levels are elevated in three-fourth of the patients.
- **Heterophile antibodies:** These nonspecific antibodies appear in over 90% of older patients with mononucleosis but in fewer than 50% of children under age 5 years. They may not be detectable until the 2nd week of illness and may persist for up to 12 months after recovery. Paul-Bunnell-Davidsohn test is positive. The test is often negative in children under 4 years of age. Heterophile antibodies, which agglutinate the sheep red cells in a titer of 1 in 56 or more are present. The high titer persists for about 3 weeks. Heterophile antibodies are immunoglobulin M (IgM) antibodies and their titer does not correlate well with severity of the illness.

Rapid screening test (slide agglutination) is usually positive result strongly suggests but does not prove EBV infection.

- **Anti-EBV antibodies:** It may be necessary to measure specific antibody titers when heterophile antibodies fail to appear, as in young children. Acute EBV infection is established by detecting IgM antibody to the viral capsid antigen (VCA) or by detecting a fall over several weeks of IgG anti-VCA titers (IgG antibody peaks by the time symptoms appear).

- **EBV PCR:** This assay detects EBV DNA. It is the method of choice for the diagnosis of CNS and ocular infections. Quantitative EBV PCR in peripheral blood mononuclear cells has been studied for the diagnosis of proliferation disorders in transplant patients.

Virus can be cultivated from oropharynx for up to a year following the acute infection.

#### LABORATORY SALIENT FINDINGS

- Atypical lymphocytosis
- Heterophile antibodies
- Anti-EBV antibodies
- EBV PCR

### DIFFERENTIAL DIAGNOSIS

Toxoplasma, Cytomegalovirus, adenovirus, rubella and hepatitis.

### TREATMENT

Bed rest may be necessary in severe cases. Acetaminophen controls high fever. Potential airway obstruction due to swollen pharyngeal lymphoid tissue responds rapidly to systemic corticosteroids.

Corticosteroids may also be given for hematologic and neurologic complications, although no controlled trials have proved their efficacy in these conditions. Fever and pharyngitis disappear by 10–14 days. Adenopathy and splenomegaly can persist several weeks longer. Some patients complain of fatigue, malaise, or lack of well-being for several months. Although steroids may shorten the duration of fatigue and malaise, their long-term effects on this potentially oncogenic viral infection are unknown, and indiscriminate use is discouraged. Patients with splenic enlargement should avoid contact sports for 6–8 weeks.

Specific antiviral therapy has generally not been beneficial in treating EBV infections, although treatment of a suspected acute *Streptococcus pyogenes* infection with a non- $\beta$ -lactam antibiotic such as clindamycin is reasonable. Regarding EBV, several nucleotide analogs have in vitro activity but have little clinical effect. Acyclovir treatment of patients with IM results in interruption of viral shedding in the throat, but clinical progression remains unaffected. However, valacyclovir has been shown to decrease the severity and number of symptoms in several studies. Prophylactic interferon- $\alpha$  decreases the incidence of EBV shedding by kidney transplant recipients but is not widely used for prophylaxis or treatment.

Lesions of oral hairy leukoplakia respond to oral or intravenous acyclovir, but they frequently recur in patients with HIV infection after treatment is discontinued. Aggressive, successful antiretroviral therapy frequently results in remission of lesions of oral hairy leukoplakia without specific treatment of EBV.

Treatment with prednisolone (1 mg/kg/day for 7 days) is advised for the complications such as hemolytic anemia, airway obstruction, meningitis, and thrombocytopenia with bleeding. Intranasal steroids may be used to relieve nasal obstruction caused by enlarged adenoids.

Acyclovir, valacyclovir, penciclovir, ganciclovir, and foscarnet are active against EBV and are indicated in the treatment of chronic active EBV.

## PREVENTION

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Ganciclovir and valganciclovir have been used to prevent post-transplant EBV disease. Two prophylactic EBV vaccines, gp350 subunit vaccine and CD8 T-cell peptide epitope vaccine, have been evaluated in clinical trials.

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## PRESENTING COMPLAINTS

A 5-year-old boy was brought with the complaints of:

- Fever since 3 days
- Headache since 2 days
- Vomiting since 1 day

## History of Presenting Complaints

A 5-year-old boy came to the hospital with history of fever, headache and vomiting.

Child had high temperature. Fever moderate to high, intermittent was associated with chills and rigors. After the chills and rigor, the boy used to sweat a lot. Later he was taken to the doctor nearby, where he was given antipyretics and antibiotics. He was afebrile for 1 day. Again, in the midnight he developed the high temperature followed by chills and rigors. The temperature recorded by the mother was 103°F. Later child started complaining of the headache. It was associated with vomiting. Next day child was brought to the hospital.

### CASE AT A GLANCE

#### Basic Findings

Height	: 107 cm (60th centile)
Weight	: 18 kg (75th centile)
Temperature	: 39°C
Pulse rate	: 110 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 90/70 mm Hg

#### Positive Findings

##### History

- Fever
- Chills and rigors
- Headache
- Vomiting

##### Examination

- Febrile
- Splenomegaly

##### Investigation

- TLC: Increased
- MP smear: Positive

## Past History of the Patient

He was second child of nonconsanguineous marriage. He was born at full term by normal delivery. There was no significant postnatal event. Child was taking breastfeeds as soon as possible. He was exclusively on breastfeeds for first 4 months. Later weaning was started. He was on family food by 18 months. He had been completely immunized. His developmental milestones were normal.

## EXAMINATION

On examination, child was moderately built and moderately nourished. His height was 107 cm (60th centile), weight was 18 kg (75th centile). He was febrile, i.e., 39°C. The pulse rate was 110 per minute, and respiratory rate was 20 per minute. Blood pressure recorded was 90/70 mm Hg. There was no pallor, no lymphadenopathy, no icterus and no edema. Per abdomen examination revealed presence of spleen measuring about 3 cm below the costal margin. It was firm and nontender. There was no other organomegaly. Other systemic examinations were normal.

## INVESTIGATIONS

Hemoglobin	: 11 g/dL
TLC	: 16,000 cells/cu mm
DLC	: $P_{72} L_{26} M_2$
Blood culture and sensitivity	: Negative
MP smear	: <i>Plasmodium vivax</i> ring and gametocyte
X-ray chest	: Normal
Urine culture and sensitivity	: Normal
WIDAL test	: Negative

## DISCUSSION

The boy has come with history of high temperature associated with chills, rigors and headache. The fever used to be intermittent and present on



Fig. 1: Cerebral malaria.

alternate days. The child used to be absolutely normal in between the attack. The history is suggestive of malaria. The malarial parasite (MP) smear was taken during the attack at the time of chills which proved MP positive (Fig. 1).

Malaria occurs when erythrocytes are invaded by any of four species of the *Plasmodium*. It is characterized by high fever which is often intermittent, anemia, and splenic enlargement.

### Life Cycle of the Malarial Parasite

**Pre-erythrocytic schizogony:** As soon as the mosquito bites, within 30 minutes, the sporozoites disappear from the blood. These will invade the liver and reticuloendothelial tissues. The parasites go through asexual reproduction in hepatic cells. Sporozoites divide and form thousands of merozoites. Merozoites will invade red cells but cannot infect hepatocytes. There are no apparent clinical symptoms during this pre-erythrocytic cycle. This phase thus constitutes the incubation period of malaria. This will be generally not less than 10 days. The process of liver schizogony lasts from 7 to 10 days for *P. falciparum*, *P. ovale*, and *P. vivax* and 10–14 days for *P. malariae*. *P. vivax* and *P. ovale* can also produce dormant liver stages (hypnozoites) that can reactivate weeks or months after the initial infection and can cause clinical relapse.

**Erythrocytic schizogony:** Merozoites invade erythrocytes. In red blood cells, they become trophozoites. The dividing stage is called erythrocytic schizont. The infected erythrocytes then rupture releasing merozoites into the circulation. The merozoites infect new erythrocytes and start the cycle all over again.

After several stages of schizogony, some merozoites develop into sexual stages, i.e., micro (male) or macro (female) gametes. When female *Anopheles* mosquito bites a patient, it sucks his

blood. Only gametocytes form survive in stomach of mosquito. The fertilized macrogamete is called zygote. The zygote enters the wall of the midgut of mosquito and during migratory stage, it is called ookinete. As it lays below outer cell layer of the stomach it is known as oocyst. Oocyst ruptures and releases sporozoites into the body cavity of the mosquito from where they migrate to salivary glands. As mosquito bites human beings it releases sporozoites into their blood.

Malaria can also be acquired by direct blood exposure through blood transfusions. Congenital malaria, with passage of infection from mother to newborn, can also occur, although it is relatively infrequent in endemic areas. It is seen more frequently in nonimmune women and in women who have an overt attack of clinical malaria during pregnancy. In areas where malaria is endemic, infection during pregnancy, even among semi-immune women, can lead to low birth weight and an increased risk of perinatal mortality.

In malaria, many organs are involved. Spleen is enlarged. Spleen is dark and shows reticular hyperplasia. It returns to normal size as the infection is controlled. In liver, there is Kupffer hyperplasia, sinusoidal and sequestration of the red blood cells (RBCs). Kidneys have ischemic tubular damage resulting in acute transient nephritis. Chronic nephrotic syndrome occurs as a result of *P. malariae*.

In cerebral malaria, there will be plugging of cerebral capillaries with infected erythrocytes, hemorrhages and deposition of fibrin in vessels. Brain capillaries, predominantly in white matter are loaded with parasite RBCs.

Disease from malaria is caused by the blood stages of the parasite. Rupture of red cells and release of merozoites into the blood lead to the fever, chills, and malaise seen in all forms of malaria. *Plasmodium*-infected erythrocytes, opsonized with antibodies or complement, are less deformable than uninfected erythrocytes and are consequently trapped in the spleen, leading to splenomegaly.

Anemia and thrombocytopenia are primarily due to splenic consumption of erythrocytes and platelets, but autoimmune hemolysis plays a role in the continued destruction of erythrocytes that can occur for weeks after appropriate treatment. In addition, bone marrow suppression occurs in severe malarial anemia, so the anemia seen is due to both erythrocyte destruction (by autoimmune hemolysis and spleen removal of infected erythrocytes) and impaired erythropoiesis.

Anemia occurs as a result of destruction of parasitized RBCs, bone marrow dysfunction, and hemolysis due to black water fever.

## CLINICAL FEATURES (FIG. 2)

Incubation period of MP varies between 9 and 30 days. The onset of disease is sudden with fever, headache and loss of appetite, lassitude and pain in the limbs. The fever may be continuous. The illness is characterized by chills and rigors, headache, nausea, malaria and anorexia, the fever occurs on alternate days.

The relapse is defined as recurrence of fever after a period which is greater than normal periodicity. Relapses are more with *Plasmodium falciparum*.

The malaria caused by *Plasmodium vivax* is a benign tertian malaria. Malaria is usually acquired from the bites of previously infected female *Anopheles* mosquitoes. Congenital malaria is caused by transfer of causative agent across the placental barrier. It is rare. Neonatal malaria, on the other hand, is less uncommon and may result from mingling of infected maternal blood with that of infant during birth process.

For clinical and diagnostic purpose, malaria may be regarded as having two disease entities. The more dangerous one is caused by *Plasmodium falciparum*. It can produce a variety of acute clinical symptoms and signs and if untreated, it proves fatal.

Children with *P. falciparum* in particular may exhibit very irregular fever patterns. Fever is present at some points in the illness in almost all nonimmune children with malaria. Seizures are

common in severe malaria. Nonimmune adults frequently exhibit the classic febrile paroxysm, which consists of three phases: a brief “cold” phase, with chills and sometimes rigors; a hot phase, with high fever, dry, flushed skin, tachypnea, and thirst; and a sweating stage, with defervescence accompanied by diaphoresis and a feeling of great relief but also great weakness. The paroxysms coincide with the rupture of infected erythrocytes and the release of merozoites, pigment, and cell debris into the circulation.

Prodromal, flulike symptoms occur during the early cycles of erythrocytic infection and may include fever (with no specific pattern), headache, malaise, myalgias, arthralgias, abdominal pain, and diarrhea. The febrile paroxysm may be extremely short or may last for 2–12 hours. Its characteristic pattern is usually observed in children less than 5 years of age. Fever may be absent or increases gradually for 1–2 days or onset may be sudden with temperature up to 40.6°C with or without prodromal chill.

Children, especially infants, may not exhibit the classic febrile paroxysm seen in adults. In infants, more nonspecific symptoms such as fever, lethargy, decreased appetite, and listlessness may continue to predominate. Vomiting, loose stools, and abdominal pain are very common complaints in both infants and children. Many infants and older children will also have intermittent fevers without a clear pattern, rather than the 48-hour (*P. vivax*, *P. ovale*, *P. falciparum*) or 72-hour (*P. malariae*) fever patterns classically described with these infections.

The physical signs most frequently seen in malaria are hepatomegaly and splenomegaly, which occur in about half of all children with acute malarial disease. In areas where malaria is highly endemic, a large percentage of children develop palpable splenomegaly over time, and the prevalence of splenomegaly in children age 2–9 years has been used to define an area’s malaria-endemicity pattern. In areas of unstable transmission and in nonimmune individuals, it is less common.

Although malaria often leads to some degree of anemia, particularly when not treated immediately, pallor is seen in only 25% of children with malaria in endemic areas and jaundice in only 10–15% of children. Scleral icterus may be seen in children. Jaundice is more common in nonimmune adults. Other physical examination findings relate to complications of malaria, such as coma or posturing in children with cerebral

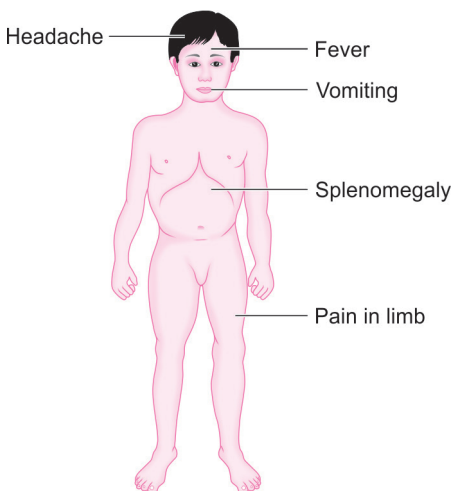


Fig. 2: Clinical features.



malaria or chest indrawing and respiratory distress in children with metabolic acidosis.

Nonimmune children with *P. falciparum* malaria often develop complications from the disease. The most common of these complications in children are severe malarial anemia, respiratory distress, and impaired consciousness. Each of these complications can contribute to and exacerbate the others, and mortality increases as the number of malarial complications increases.

## Cerebral Malaria

By the definition, cerebral malaria is present in a patient who (1) cannot localize a painful stimulus, (2) has peripheral asexual *P. falciparum* parasitemia, and (3) has no other causes of an encephalopathy. The pathophysiology of impaired consciousness in a child with severe malaria is likely the same as that of coma.

Cerebral malaria often develops rapidly. Parents typically give a history of 2–5 days of fever, followed by abrupt onset or convulsions or severely impaired consciousness. Children with cerebral malaria may progress from a normal sensorium to coma within hours. Focal seizures are occasionally seen, but focal neurologic deficits are rare. Meningeal signs are usually absent—abnormal posturing, papillary changes, absent corneal reflexes, Cheyne-Stokes or Kussmaul respirations, and gaze abnormalities may be seen.

Malaria retinopathy consists of four main components: retinal whitening vessel changes, retinal hemorrhages, and papilledema. Retinal whitening and the vessel color changes are specific to malaria and are not seen in other ocular or systemic conditions. Papilledema is an independent indicator of poor outcome. Malaria retinopathy appears to distinguish children with cerebral malaria from those with coma due to other causes but is impractical as a standard diagnostic tool because it must be assessed with indirect ophthalmoscopy.

In addition, children who meet WHO criteria for cerebral malaria but do not have retinopathy may still have *P. falciparum* as the primary cause of coma. For this reasons, retinopathy is not a requirement for diagnosis of cerebral malaria. Increased intracranial pressure (ICP), generally not seen in adults with cerebral malaria, is a feature of cerebral malaria in children. Studies of interventions that decrease ICP in children with cerebral malaria, including steroids and mannitol, have not shown improved outcomes to date,

so understanding and addressing the root cause of increased brain swelling in children with cerebral malaria are key to better outcomes in these children.

Nonimmune adults can develop neurologic sequelae after severe malaria, even without cerebral malaria. Neurologic sequelae seen in nonimmune adults may also be seen in nonimmune older children and may include cranial nerve defects, mononeuritis multiplex, polyneuropathy, and cerebellar dysfunction.

### ESSENTIAL DIAGNOSTIC POINTS

- Fever in endemic area
- Paroxysms of chills, fever and sweating
- Splenomegaly, anemia
- Headache, vomiting, and diarrhea
- Backache, cough, abdominal pain
- Seizures and coma
- Malarial parasite in peripheral blood smear

Severe complicated malaria is caused by *P. falciparum*. It is attributed to the high parasitemia, cytoadherence, sequestration. The manifestation include:

- Cerebral malaria
- Severe anemia
- Acute renal failure
- Pulmonary edema or acute respiratory distress syndrome (ARDS)
- Hypoglycemia
- Shock
- Disseminated intravascular coagulation (DIC) and repeated generalized convulsions

*Blackwater fever* is characterized by sudden massive intravascular hemolysis and passage of high coloured urine due to hemoglobinuria. Renal failure may develop. It occurs in G6PD deficiency anemia.

## Congenital Malaria

It occurs in nonimmune mother. Congenital malaria is caused by transfer of causative agent across the placental barrier. It is probably due to the transplacental transfer of protective maternal immunoglobulin G (IgG) antibodies. The incubation period ranges from 2 to 8 weeks. Clinical manifestation include fever irritability, failure to thrive, pallor, jaundice and hepatosplenomegaly.

Chronic complications include tropical splenomegaly, nephritic syndrome, endemic Burkitt's lymphoma, endomyocardial fibrosis. Relapses are not seen with *P. falciparum* and *P. malaria* as there is no persistent exoerythrocytic cycles.

**GENERAL FEATURES**

- Sudden onset
- Loss of appetite
- Chills with rigors
- Sweating
- Convulsions

**DIAGNOSIS****Microscopic Diagnosis (Fig. 3)**

The gold standard for diagnosis of malaria is careful examination of a properly prepared thick film. Thick smears have as sensitivity of detecting 5–10 parasites/μL. Thin smears have a lower sensitivity of 200 parasites/μL but enable species identification. Microscopy also provides information about the parasite load (number of infected RBC/total RBC), prognosis (mature schizonts and pigmented neutrophils indicating a poor prognosis) and tracks response to therapy. The main drawback is need for expertise, and that they are time consuming (a careful examination of 100 fields needs 20 minutes). Sometimes peripheral smears may be negative due to partial antimalarial treatment or sequestration of parasitized cells in deep vascular beds. Repeating smears every 6–8 hourly at least three times is recommended if the clinical suspicion for malaria is high and the initial smear is negative.

Sample collection should be done as soon as malaria is suspected. It can be collected any time irrespective of fever and not necessarily only at the height of fever. Collection should be before administration of antimalarials, which causes

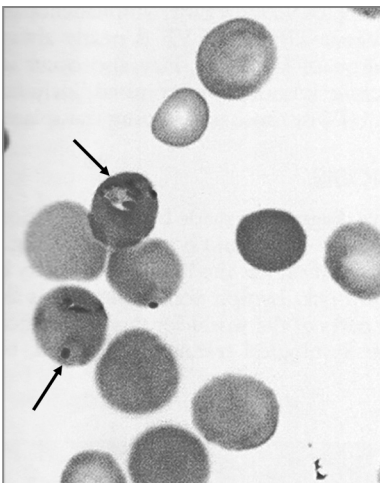
detection of parasites difficult due to its morphologic alteration.

Examination of Giemsa-stained thick and thin blood smears remains the primary method for diagnosis of malaria. Thick smears are more sensitive in detecting parasites, but thin smears are necessary for identifying *Plasmodium* species and allow estimation of the degree of peripheral blood parasitemia.

It is most important to distinguish *P. falciparum* from the other four human malaria species. *P. falciparum* malaria is suggested by parasitemia that exceeds 2% of red cells, red cells that contain multiple parasites, the almost exclusive presence of ring forms of the parasite, ring forms with a double chromatin dot, and the presence of parasites in all ages of red cells. The banana-shaped gametocyte is pathognomonic for *P. falciparum* malaria. *P. malariae* is characterized by low-level parasitemia and a characteristic band trophozoite. Schuffner's stippling is characteristic of *P. vivax* and *P. ovale*, although it may be more subtle in *P. ovale* infections. *P. ovale*-infected cells often have an oval shape in addition to the stippling.

*Quantitative buff coat (QBC) test* is a new method for identifying the MP in the peripheral blood. It involves staining of the centrifuged and compressed red cell layer with acridine orange and its examination under ultraviolet (UV) light source. It is fast, easy and claimed to be more sensitive than the traditional thick smear examination.

Disadvantages include need for special equipment, cost, false positives due to staining artifacts and inability to speciate the parasite. QBC has been largely supplanted by the rapid diagnostic tests detailed here.



**Fig. 3:** Peripheral blood smear.  
(For color version see Plate 4)

**Rapid Diagnosis Tests**

These are immunochromatographic tests (ICT) to detect *Plasmodium* specific antigens in blood sample. They employ monoclonal antibodies directed against targeted parasite antigens. In our country, where *falciparum* and *vivax* malaria parasites co-circulate, typically occurring as a single species infection, a rapid diagnostic test (RDT) which can detect both *falciparum* and *vivax* malaria and distinguish between them is warranted.

**Other Methods of Diagnosis**

Other diagnostic methods namely microscopy-using fluorochromes on centrifuged blood specimens, molecular probes, polymerase chain reaction (PCR) and serology are available. Unfortunately,

they are not suitable for routine disease management and do not have wide field application. Their use is currently for only research and epidemiological purposes.

Polymerase chain reaction has been found to be highly sensitive and specific for detecting all species of malaria, particularly in cases of low level parasitemia but is not available commercially and hence of limited practical utility.

#### LABORATORY SALIENT FINDINGS

- Giemsa-stained thick smears
- Enzyme-linked immunosorbent assay (ELISA)
- DNA hybridization
- Polymerase chain reaction
- Reflection of severity: decreased hematocrit, Hb, haptoglobin levels, increased reticulocyte count, increased LDH levels
- Thrombocytopenia

### COMPLICATIONS

- Cerebral malaria
- Liver failure
- Anemia
- Jaundice
- Shock
- Pulmonary edema
- Dehydration

### DIFFERENTIAL DIAGNOSIS

- Typhoid
- Hepatitis
- Septicemia
- Urinary tract infection
- Meningitis
- Encephalitis

### TREATMENT

Management includes symptomatic treatment and as well as specific treatment. Fluids and electrolytes are given intravenously to maintain hydration.

All ill-appearing children should be considered nonimmune. Children less than 5-year-old, children traveling to or from malaria endemic areas but originally from a nonendemic area, and children who have been away from an endemic area for more than 6 months should be considered nonimmune. In many malaria-endemic countries, there are large cities where little or no malaria transmission occurs, and individuals from these cities are essentially nonimmune. A well-appearing child over 5 years of age who has arrived within 6 months from a malaria-endemic area but who

has *Plasmodium* species infection on blood smear may be considered semi-immune.

*Plasmodium falciparum* malaria can be a life-threatening emergency, especially in the nonimmune individual. Any child from a malaria-endemic area with signs and symptoms of severe malaria should be treated for falciparum malaria while awaiting blood smear confirmation. Non-immune children with documented *P. falciparum* malaria should be hospitalized, because clinical decompensation can occur rapidly, even in children with a relatively benign initial presentation. Nonimmune children with *P. vivax*, *P. ovale*, or *P. malariae* infection can appear quite ill with the initial paroxysm and also typically require hospitalization.

Supportive therapy includes fluid and electrolyte balance. Dehydration and shock is corrected. Packed red cells are transfused. Renal failure and seizures are managed accordingly.

### Uncomplicated Malaria

Chloroquine 10 mg of base/kg is given stat. This is followed by 5 mg of the base/kg at 12, 24, and 36 hours intervals. Patients with vivax and ovale malaria should be given 0.25 mg/kg daily for 14 days to prevent relapse.

*Malaria due to P. vivax, P. ovale, P. malariae, and P. knowlesi:* Complications due to *P. vivax*, *P. ovale*, or *P. malariae* are less common than with *P. falciparum*, and severe disease is consequently less common as well, but all malaria species can cause significant illness in a nonimmune child, and in some areas, *P. vivax* is a more common cause of severe illness than *P. falciparum*. Coinfection with *P. falciparum*, may be missed on blood smear if the slide reader is inexperienced or if the infection inoculum is low. Children hospitalized with nonfalciparum malaria should be given the same drug treatment regimen as children hospitalized for falciparum malaria.

The guidelines recommend chloroquine or hydroxychloroquine treatment for malaria due to *P. vivax*, *P. ovale*, *P. knowlesi*, and *P. malariae*. Prior to treatment with primaquine, all patients should be screened for G6PD deficiency. Individuals with the severe form of G6PD deficiency may experience an oxidant hemolysis and methemoglobinemia with primaquine administration and should not receive primaquine. There are currently no effective alternatives to primaquine for liver-stage parasite eradication. Although scattered reports of *P. ovale*

and *P. malariae* chloroquine-resistance exist, resistance is not widespread and chloroquine remains first-line therapy for these parasites.

### Chloroquine-resistant Malaria

Quinine 7 mg/kg IV infusion over 4 hours followed by 10 mg/kg infused over 2–8 hours at 8 hourly interval until the patient can swallow. The 7-day course should be completed with quinine tablets are syrup 10 mg/kg three times a day.

- Artemether 3.2 mg/kg IM stat followed by 1.6 mg/kg at 24-hour interval for 6 days.
- Artesunate 2.4 mg/kg stat by IV injection followed by 1.2 mg/kg after 12 hours, and then 1.2 mg/kg daily for 6 days.

### *Plasmodium falciparum* Malaria

Intravenous quinidine remains the drug of choice for all children with *P. falciparum* malaria who require hospitalization. Artesunate is recommended by the World Health Organization (WHO) in preference to quinidine for the treatment of severe malaria based on studies showing a lower mortality in children with severe malaria treated with artesunate. Artesunate has been used worldwide for many years. Treating *P. falciparum* infection with quinine, quinidine, artesunate, or artemether alone has been associated with significant recrudescence rates, which are decreased with the addition of doxycycline, tetracycline, or clindamycin. High-level quinine resistance, although reported, remains uncommon.

The potential cardiac toxicity of quinidine necessitates that patients receive it as an intravenous infusion, never as a bolus, while on continuous electrocardiographic monitoring. Infusion rates should be reduced if the QT interval is prolonged by more than 25% of the baseline value. Both quinine and quinidine can induce hyperinsulinemic hypoglycemia, which may cause lethargy or unresponsiveness that is confused with cerebral malaria; therefore, glucose levels should be followed in severely ill patients who are on these medications. Long-term side effects from either medication are uncommon, and the cinchonism (nausea, dysphoria, tinnitus, and high-tone deafness) seen with quinine resolves with cessation of quinine therapy.

When children are ready for oral therapy guidelines suggest completion of the course with oral quinine plus doxycycline, tetracycline, or clindamycin. However, many children do not tolerate oral quinine well, and in practice, a full course of artemether-lumefantrine, now available

in the United States, is often given instead of quinine.

Adjunctive treatment for severe malaria includes blood transfusion for children with severe malarial anemia, seizure medication for children with repeated seizures, and intravenous antibiotics in children with hypotension or other signs of sepsis. Exchange transfusion for hyperparasitemia is controversial. Some guidelines still recommend exchange transfusion for parasitemia >10%, but a recent review concluded that there was little evidence to suggest benefit to patients from exchange transfusion.

### Uncomplicated *Plasmodium falciparum* Malaria

#### *Chloroquine Resistant*

Artemether-lumefantrine and atovaquone-proguanil are the preferred alternatives to quinine treatment for uncomplicated chloroquine-resistant *P. falciparum* malaria. It has few side effects, and the side effects of atovaquone-proguanil (abdominal pain, vomiting, nausea, and headache) are usually mild and self-limited. In some studies, an elevation of transaminases was seen with atovaquone-proguanil treatment, but transaminase elevations have not been associated with untoward clinical events. Atovaquone-proguanil should be taken with food or a milky drink. Vomiting occurs within 1 hour of dosing of artemether-lumefantrine, a repeat dose should be given. Because atovaquone-proguanil is also used for prophylaxis, it is typically more easily available than artemether-lumefantrine. Children who took atovaquone-proguanil for malaria prophylaxis should not receive it for treatment of malaria. Instead, artemether-lumefantrine, or, if artemether-lumefantrine is not immediately available, quinine or mefloquine, should be used in children who have received atovaquone-proguanil prophylaxis.

Oral quinine plus doxycycline, tetracycline, or clindamycin can also be used for treatment of uncomplicated chloroquine-resistant *P. falciparum* infection but has significantly more side effects than artemether-lumefantrine or atovaquone-proguanil.

Children frequently vomit after receiving quinine, especially if they are febrile when receiving the drug. Acetaminophen and sponge hinge prior to administration of oral quinine may decrease the likelihood of vomiting. If vomiting occurs within an hour, the full dose of quinine

should be repeated if vomiting occurs after 1 hour, no repeat quinine dosing is necessary. Other side effects of quinine are as noted above. In situations, where urgent treatment is required and intravenous medications cannot be given, intrarectal or intramuscular quinine has been used successfully.

Mefloquine can be used to treat chloroquine-resistant-malaria, but increasing mefloquine resistance, and significant CNS side effects with treatment dosages make it an inferior choice, to be used only when artemether-lumefantrine, atovaquone-proguanil, or quinine treatment is not an option. Mefloquine should not be used if the child took mefloquine as prophylaxis, and it should not be used in conjunction with quinine or quinidine, as it may potentiate the cardiac side effects of these medications.

Mefloquine is used in the dose of 15 mg base/kg orally stat and repeated 8–24 hours after, in the dose of 10 mg/kg, i.e., two doses only.

Halofantrine is used in mefloquine-resistant cases. It is used in the dose of 8 mg/kg given three times at 6–8 hours intervals for 3 days.

### *Chloroquine-sensitive*

Chloroquine remains the drug of choice for chloroquine-susceptible *P. falciparum* malaria. It is inexpensive, generally well tolerated, and easy to administer. Side effects include pruritus in dark-skinned patients (which is fairly common) and, in treatment doses, nausea, dysphoria, and rarely a transient neuropsychiatric syndrome or cerebellar dysfunction. Hydroxychloroquine may be

used if chloroquine is not available. If there is any doubt as to whether chloroquine resistance is present in the area, malaria was acquired, quinine should be used. Quinidine is the preferred drug in the United States for parenteral treatment of chloroquine-sensitive malaria.

*Cerebral malaria:* Chloroquine is used at the dose of 10 mg/kg IV infusion in 0.9% saline, intravenous fluid such as 5% or 10% dextrose 10 mg/kg as maintenance dose.

*Treatment of relapse:* It requires the specific therapy with a combination of chloroquine followed by primaquine for 10–14 days. Treatment of relapsing malaria (*P. vivax* and *P. ovale*) is treated with standard course of chloroquine followed by primaquine 0.25 mg/kg orally per day for 14 days.

*Prophylaxis:* Chloroquine is used 5 mg/kg given orally every week. In prophylaxis in chloroquine resistant area, mefloquine (3.5 mg base/kg weekly) or doxycycline 2 mg/kg daily is given.

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## PRESENTING COMPLAINTS

A 10-month-old girl was brought with the complaints of:

- Cold and cough since 5 days
- Fever since 5 days
- Rashes since 1 day

## History of Presenting Complaints

A 10-month-old girl was brought to the pediatric outpatient department with history of rashes all over the body. Her mother told that the child had cough, cold and fever 3 days back. Child was on symptomatic and antibiotic treatment. Fever was of mild-to-moderate degree. Mother had also told the temperature was not coming down in spite of antipyretics. Child was also having cough and cold. Cold was associated with nasal block and she had feeding problems. Cough used to be more in night, hence child had disturbed sleep. On the 4th day, mother noticed the small red colored rashes over the trunk, abdomen and back. Rashes were not elevated over the skin. There was no itching.

### CASE AT A GLANCE

#### Basic Findings

Length	: 70 cm (50th centile)
Weight	: 7.5 kg (50th centile)
Temperature	: 39°C
Pulse rate	: 126 per minute
Respiratory rate	: 28 per minute
Blood pressure	: 60/46 mm Hg

#### Positive Findings

##### History

- Fever
- Cough and cold
- Rashes

##### Examination

- Febrile
- Signs of dehydration
- Sick look
- Rashes

##### Investigation

- Chest X-ray: Signs of bronchopneumonia

## Past History of the Patient

The girl was the first sibling of nonconsanguineous marriage. She was born at term by normal vaginal delivery. The baby cried immediately after the delivery. The birth weight was 3 kg. Child started taking the breast milk immediately. There was no significant postnatal event. Baby was exclusively on breastfeeds for 3 months. Developmental milestones were normal.

## EXAMINATION

Child was moderately built and nourished. She was looking sick and irritable. Signs of mild dehydration were present. Anthropometric measurements included, the length was 70 cm (50th centile) and weight was 7.5 kg (50th centile). The head circumference was 43 cm.

The child was febrile, i.e., 39°C. The heart rate was 126 per minute, the respiratory rate was 28 per minute. Blood pressure recorded was 60/46 mm Hg. There was no pallor, no lymphadenopathy, no edema and cyanosis. There were signs of rhinitis.

Respiratory system revealed presence of crepitation at the base. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 7,600 cells/cu mm
DLC	: P <sub>73</sub> L <sub>25</sub> E <sub>2</sub>
ESR	: 26 mm in the 1st hour
AEC	: 430 cells/cu mm
Chest X-ray	: Signs of bronchopneumonia

## DISCUSSION

It is a communicable disease characterized by fever, cough, coryza and Koplik's spots in the pre-eruptive phase. Maculopapular rashes appear on 4th and 5th day of the illness.

Measles virus is a spherical, nonsegmented, single-stranded, negative sense ribonucleic acid (RNA) virus and a member of the *Morbillivirus* genus

in the family of paramyxoviridae. Measles was originally a zoonotic infection, arising from cross-species transmission from animals to humans by an ancestral *Morbillivirus*. Although RNA viruses typically have high mutation rates, measles virus is considered to be an antigenically monotypic virus, meaning that the surface proteins responsible for inducing protective immunity have retained their antigenic structure across time and space.

Measles virus is transmitted primarily by respiratory droplets over short distances and less commonly, by small-particle aerosols that remain suspended in the air for long periods of time. Airborne transmission appears to be important in certain settings, including schools, pediatrician offices, hospitals, and enclosed public places, and infectious droplets may persist for several hours after an infected child has left a pediatrician's office. Direct contact with infected secretions can transmit measles virus, but the virus does not survive long on fomites. The disease is more common in pre-school children and occurs in all seasons. It is more in winter and spring months.

Infection is initiated when measles virus reaches epithelial cells in the respiratory tract, oropharynx, or conjunctivae. Wild-type measles virus strains preferentially bind to SLAM (CD150), expressed on activated T cells, B cells, and antigen-presenting cells, whereas laboratory-adapted strains can also bind CD46, which is expressed on all nucleated cells.

Measles virus thus infects lymphocytes and dendritic cells, as well as respiratory epithelial cells, which contributes to systemic spread. During the first 2–4 days after infection, measles virus proliferates locally in the respiratory mucosa and spreads to draining lymph nodes where further replication occurs. Virus then enters the bloodstream in infected leukocytes, primarily monocytes, producing the primary viremia that disseminates infection throughout the reticuloendothelial system.

Further replication results in a secondary viremia that begins 5–7 days after infection and disseminates measles virus to tissues throughout the body. Replication of measles virus in these target organs, together with the host immune response, is responsible for the signs and symptoms that occur 8–12 days after infection and mark the end of the incubation period.

The incubation period for measles, the time from infection to clinical disease, is approximately 10 days to the onset of fever and 14 days to the onset of rash. The incubation period may be shorter in infants or following a large inoculum

of virus and may be longer (up to 3 weeks) in adults.

## **PATHOLOGY**

Measles is caused by RNA *Paramyxovirus*. There is only one serotype. The virus cannot survive outside the human body, for any length or time but retains the infectivity when stored at sub-zero temperature. The only source of infection is measles case. Carriers are not known to occur. The infective materials include secretion of the nose, throat and respiratory tract during the prodromal period and early stages of rash.

Measles is highly infectious during the prodromal period and at the time of eruption. Communicability declines rapidly after the appearance of rash. The period of communicability is approximately 4 days before and 5 days after the appearance of rash. Isolation of the patient for a week from the onset of rash covers the period of communicability. As there is one antigenic type of measles virus infection, confers lifelong immunity. Hence so called secondary attacks represents the error in diagnosis.

Cells are killed by cell-to-cell plasma membrane fusion associated with viral replication that occurs in many body tissues, including cells of the central nervous system. Virus shedding begins in the prodromal phase. With onset of the rash, antibody production begins, and viral replication and symptoms begin to subside.

Diseases other than measles that have been associated with measles virus include subacute sclerosing panencephalitis (SSPE), multiple sclerosis, cirrhosis disease, Paget's disease, and systemic lupus erythematosus (SLE).

There is generalized hyperplasia of the lymphoid tissue. Lesions include superficial vessels of corium of skin and in capillary bed of the mucosa. There is perivascular infiltration with mononuclear and polymorphonuclear leukocytosis. Frank vesicles are formed. Multinucleated giant cells infiltrate into the lymphoid tissue. Multinucleated giant cells are found. There are two types: Warthin–Finkeldey cells of reticuloendothelial system and epithelioid giant cells of respiratory system. Inclusion bodies may be seen in brain cells, cerebrospinal fluid (CSF) examination shows pleocytosis. Lungs may show peribronchial inflammatory reaction with mononuclear cells, giant cell, pneumonia, and secondary bacterial pneumonia.

Measles tend to be more severe in malnourished child. This may be related to poor

cell-mediated immunity response secondary to malnutrition. They excrete measles virus for longer periods indicated prolonged risk for themselves and of intensity of spread to others. Local multiplication in respiratory epithelium leads to viremia (days 2–3) and subsequently spread to reticulo-endothelial system. Cells of reticuloendothelial system necrose causing secondary viremia (days 5–7). This is responsible for systemic symptoms.

### CLINICAL FEATURES (FIG. 1)

Actually everyone in infancy or childhood between 6 months and 3 years of age in developing countries are vulnerable for disease. No age is immune if there was no previous immunity. Infants are protected by maternal antibodies up to 6 months of age and on some cases the maternal immunity may persist beyond 9 months. Immunity after the vaccination is solid and long-lasting.

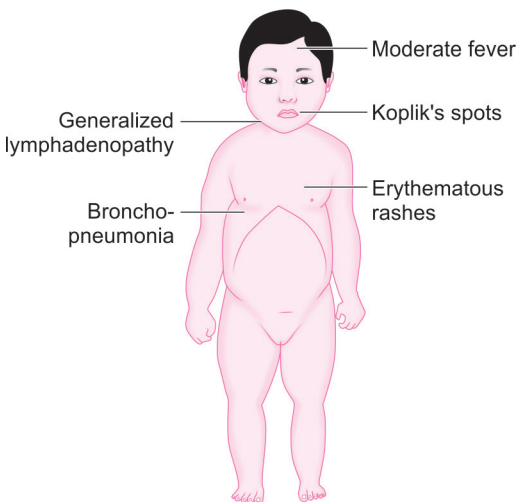
In individuals with passively acquired antibody, such as infants and recipients of blood products, a subclinical form of measles may occur. The rash may be indistinct, brief, or, rarely, entirely absent. Likewise, some individuals who have received vaccine, when exposed to measles, may have a rash but few other symptoms. Persons with inapparent or subclinical measles do not shed measles virus and do not transmit infection to household contacts.

There are three stages in the clinical features as follows:

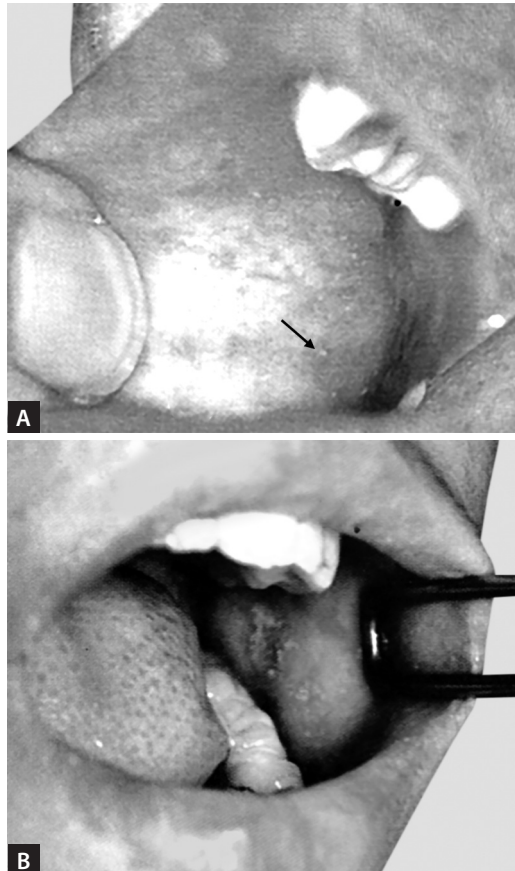
1. *Prodromal stage:* Measles is a serious infection characterized by high fever, an enanthem, cough, coryza, conjunctivitis, and a prominent

exanthem. After an incubation period of 8–12 days, the prodromal phase begins with a mild fever followed by the onset of conjunctivitis with photophobia, coryza, a prominent cough, and increasing fever. Koplik's spots (**Figs. 2A and B**) represent the enanthem and are the pathognomonic sign of measles, appearing 1–4 days prior to the onset of the rash. They first appear as discrete red lesions with bluish white spots in the center on the inner aspects of the cheeks at the level of the premolars. They may spread to involve the lips, hard palate, and gingiva. They also may occur in conjunctival folds and in the vaginal mucosa. Koplik's spots (**Figs. 2A and B**) have been reported in 50–70% of measles cases but probably occur in the great majority.

Anorexia and malaise are often accompanied. Moderate generalized lymphadenopathy is also seen. Bleeding occurs from the mouth, nose and bowel and many result in death.



**Fig. 1:** Clinical features.



**Figs. 2A and B:** Koplik's spots.  
(For color version see Plate 4)

2. *Eruptive phase*: Symptoms increase in intensity for 2–4 days until the 1st day of the rash. Typically the rash appears on the 4th day of the fever. This is characterized by typical, macular or maculopapular rashes (**Fig. 3**). The rash first appears behind the ear, then trunk and extremities. Later it extends down the body and lower limbs within 2–3 days. The rash may become discrete. In the absence of complication, the rash and fever will disappear in another 4–5 days. The rash fades in the same order of appearance leaving a brownish discoloration which may persist for 2 months. The rash is erythematous and blanches on pressure. Fever and rash may remain for about a week in uncomplicated cases. Rash may be atypical in few cases. It may be modified to hemorrhagic type. Hemorrhagic measles is characterized by high fever convulsion, delirium, stupor and even coma. Of the major symptoms of measles, the cough lasts the longest, often up to 10 days. In more severe cases, generalized lymphadenopathy may be present, with cervical and occipital lymph nodes especially prominent.
3. *Postmeasles stage*: There will be loss of weight. Child may be failure to recover and there will be gradual deterioration into chronic illness due to increased susceptibility to other bacterial and viral infection. There may be growth retardation and diarrhea, cancrum oris, pyogenic infection, candidosis, reactivation of pulmonary tuberculosis. Modified measles is seen in partially immune individuals. The symptoms are milder and duration of illness is shorter.



**Fig. 3:** Maculopapular rashes.  
(For color version see Plate 4)

#### GENERAL FEATURES

- Dry hacking cough
- Cold and sneezing
- Anorexia, malaise
- Bronchopneumonia
- Encephalitis
- Subacute sclerosing panencephalitis (SSPE)
- Malnutrition

#### ESSENTIAL DIAGNOSTIC POINTS

- Contact with measles 10–14 days back
- Fever, cough, conjunctivitis and coryza
- Koplik's spots 1–2 days prior to and after onset of rash
- Maculopapular rash spreading down from the face and hairline to the trunk over 3 days and later becoming confluent
- Leukopenia

### DIAGNOSIS

Measles is readily diagnosed on clinical grounds by clinicians familiar with the disease. Koplik's spots are especially helpful because they appear early and are pathognomonic of measles. The case definition for measles requires: (i) a generalized maculopapular rash of at least 3 days in duration; (ii) fever of at least 38.3°C (101°F); and (iii) cough, coryza, or conjunctivitis.

Serology is the most common method of laboratory diagnosis. A positive immunoglobulin M (IgM) on a single serum specimen or a significant increase in serum IgG antibody concentration in paired acute and convalescent serum specimens (collected at least 10 days apart) on a patient with clinical manifestations consistent with measles is considered diagnostic of acute infection. Measles virus-specific IgM antibodies may not be detectable until 4–5 days or more after rash onset and usually fall to undetectable levels within 4–8 weeks of rash onset.

Commercially available enzyme immunoassays (EIAs) can detect either IgM or IgG antibodies to measles virus and are the most frequently used diagnostic methods.

#### LABORATORY SALIENT FINDINGS

- ELISA
- Hemagglutination tests
- IgM antibodies
- Lymphopenia

Measles can also be diagnosed by isolation of measles virus or identification of measles RNA by reverse transcription polymerase chain reaction (RT-PCR) amplification of RNA extracted from clinical specimens, such as urine, blood, or throat or nasopharyngeal secretions.

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes rubella, infectious mononucleosis, meningococcemia, and typhoid.

## COMPLICATIONS

A wide variety of complications may be observed during the acute stage of measles or shortly thereafter.

A benign asymptomatic keratoconjunctivitis that accompanies measles may persist for as long as 4 months. More severe corneal lesions occur in malnourished children. Transient electrocardiographic abnormalities are common, but true myocarditis is rare. The diffuse lymphadenopathy that accompanies measles involves the mesenteric nodes and is believed to cause the abdominal pain that commonly occurs. Symptoms and signs identical to those of acute appendicitis may result in surgical intervention during the prodromal period.

Complications of bacterial origin result principally from invasion of the respiratory tract by pyogenic organisms. Otitis media and bronchopneumonia are most common. Peribronchitis and interstitial pneumonitis are seen in nearly all children with measles and resolve rapidly after the development of rash and the subsidence of fever. The respiratory tract is involved most often, but severe gastroenteritis also occurs. Acute laryngotracheobronchitis (croup) may cause sufficient airway obstruction to require tracheostomy, especially in children younger than 3 years.

A second fever spike, or failure of the initial spike to drop after the eruption has reached its peak, suggests a secondary bacterial infection. A chest radiograph may disclose bronchopneumonia or a pattern of segmental or lobar involvement.

During the early viremic phase of measles, there is a thrombocytopenia of insufficient magnitude to cause spontaneous bleeding. Another rare and unexplained postinfectious complication, thrombocytopenic purpura, appears 4–14 days after the rash and may produce marked skin purpura, genitourinary and gastrointestinal bleeding, and epistaxis.

Acute postinfectious measles encephalomyelitis is the most common neurologic complication of measles. It is rare in children younger than 2 years, but occurs in about 1 in 1,000 cases of measles in older children and somewhat more frequently in adults. The onset is usually during the 1st week after the start of the rash and is typically abrupt, with irritability, headache, vomiting, and

confusion, and progressing rapidly to obtundation and coma. These manifestations are frequently accompanied by seizures and recurrence or accentuation of fever.

Subacute sclerosing panencephalitis is a chronic complication of measles with a delayed onset and an outcome that is nearly always fatal. It appears to result from a persistent infection with an altered measles virus that is harbored intracellularly in the central nervous system (CNS) for several years. After 7–10 years the virus apparently regains virulence and attacks the cells in the CNS that offered the virus protection. This “slow virus infection” results in inflammation and cell death, leading to an inexorable neurodegenerative process.

Convalescence is prolonged with respiratory complication. Death may occur. The cause of death may be measles encephalopathy and may be left with severe neurological deficiency.

## TREATMENT

Treatment is essentially symptomatic and supportive. Antiviral therapy is not effective in the treatment of measles in otherwise normal patients. Maintenance of hydration, oxygenation, and comfort are goals of therapy. Child should be given adequate amount of fluids orally. Nutrition of the patient should be maintained. If there is vomiting, intravenous fluid should be given. Fever is controlled by paracetamol and hydrotherapy. Cough may be treated by humidification and saline nebulization. Treatment of the respiratory complications includes antibiotics, oxygen and supportive measures. Convulsions are managed by injections of diazepam and phenobarbitone.

Secondary bacterial infections are a major cause of morbidity and mortality following measles, and effective case management involves prompt treatment with antibiotics. Antibiotics are indicated for children with measles who have clinical evidence of bacterial infection, including pneumonia and otitis media. *Streptococcus pneumoniae* and *Haemophilus influenzae* type B were the most common causes of bacterial pneumonia following measles, and vaccines against these pathogens have lowered the incidence of secondary bacterial infections following measles.

Prophylactic antimicrobial therapy to prevent bacterial infection is not indicated. Measles infection in immunocompromised patients is highly lethal. Ribavirin is active in vitro against measles virus.



Vitamin A treatment results in marked reductions in morbidity and mortality. Currently, the World Health Organization (WHO) recommends vitamin A for all children with acute measles, regardless of their country of residence. Vitamin A for treatment of measles is administered once daily for 2 days, at the following doses: 200,000 IU for children 12 months or older; 100,000 IU for infants 6 through 11 months of age; and 50,000 IU for infants younger than 6 months. An additional (i.e., third dose) age-specific dose should be given 2–4 weeks later to children with clinical signs and symptoms of vitamin A deficiency.

## PREVENTION

Measles vaccine should not be used in patients with leukemia, lymphopenia, steroid therapy, and antimetabolic therapy. Passive immunization is

done in exposed infants and younger siblings. Gamma globulin is injected intramuscularly. The doses 0.25 mL/kg for children less than 1 year and 0.5 mL/kg for children more than 1 year, respectively.

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## PRESENTING COMPLAINTS

An 8-year-old boy was brought with the complaints of:

- Fever since 3 days
- Swelling on both the cheeks since 3 days

## History of Presenting Complaints

An 8-year-old boy was brought by mother with history of swelling on both the cheeks. Mother told, his son developed swelling first on the right side below the ear lobe and later on the left side. There was also associated history of fever. Fever was moderate to high degree intermittent in nature and was more in the evening. Child was taking treatment for the fever.

## Past History of the Patient

He was the elder sibling of nonconsanguineous marriage. He was born at term by normal vaginal delivery. There was no significant postnatal event. He was exclusively on breast milk for 4 months. Weaning was started later as per the advice of family doctor. Child was on family food by 18 months. He had been completely immunized

and all the developmental milestones were normal. His performance at school was good. There was also history of similar type of illness in his class. There was no history of rashes over the body.

## EXAMINATION

The boy was moderately built and nourished. He was sitting comfortably on examination table. Anthropometric measurements included, the height was 123 cm (50th centile), and the weight was 25 kg (75th centile). He was febrile, i.e., 38.6°C. The heart rate was 110 per minute, the respiratory rate was 26 per minute, and blood pressure recorded was 80/60 mm Hg. There was no pallor, no lymphadenopathy, no cyanosis and no icterus.

There was diffuse swelling at angle of mandible involving parotid glands on both sides. It was tender. Other systemic examinations were normal.

## INVESTIGATIONS

Hemoglobin	: 13 g/dL
TLC	: 9,900 cells/cu mm
DLC	: $P_{67} L_{30} E_2 M_1$
ESR	: 26 mm in the 1st hour
AEC	: 330 cells/cu mm
Mantoux test	: Negative
X-ray chest	: NAD

## DISCUSSION

Mumps is an acute viral infection characterized for painful enlargement of the salivary gland especially parotid gland. Mumps virus is a ribonucleic acid (RNA) virus. It spreads from the human reservoir by direct contact or air-borne droplets. The causative agent is myxovirus parotitis. There is only one serotype.

Infants are rarely involved due to the presence of transplacentally-acquired maternal mumps antibodies. Carrier state does not exist. Lifelong immunity follows the clinical attack.

Mumps virus is in the family Paramyxoviridae and the genus *Rubulavirinae*. It is a single-stranded

### CASE AT A GLANCE

#### Basic Findings

Height	: 123 cm (50th centile)
Weight	: 25 kg (75th centile)
Temperature	: 38.6°C
Pulse rate	: 110 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 80/60 mm Hg

#### Positive Findings

##### History

- Fever
- Swelling at cheeks
- Similar complaints in school

##### Examination

- Febrile
- Parotid gland swelling

##### Investigation

- Normal

pleomorphic RNA virus encapsulated in a lipoprotein envelope and possessing seven structural proteins. Surface glycoproteins called HN (hemagglutinin-neuraminidase) and F (fusion) mediate absorption of the virus to host cells and penetration of the virus into cells, respectively. Both of these proteins stimulate production of protective antibodies. Mumps virus exists as a single immunotype, and humans are the only natural host.

## **PATHOLOGY AND PATHOGENESIS**

Mumps is a communicable, systemic viral illness most often characterized by parotitis. Mumps virus is a paramyxovirus closely related to parainfluenza viruses. Mumps is spread by respiratory droplet or through direct contact with saliva. The virus can be isolated from saliva up to 7 days before and through 8 days after parotid swelling.

It commonly occurs between the age of 5 and 15 years. Man is the reservoir of the infection. Saliva is highly infective. Inoculation is by direct contact in infants below the age of 6 months is immune because of maternal antibodies.

The virus enters through the nose and mouth and proliferates in parotid gland and respiratory mucosa. This is followed by viremia. Following infection, initial viral replication occurs in the epithelium of the upper respiratory tract. Infection spreads to the adjacent lymph nodes by the lymphatic drainage, and viremia ensues, spreading the virus to targeted tissues. Mumps virus targets the salivary glands, central nervous system (CNS), pancreas, testes, and to a lesser extent, thyroid, ovaries, heart, kidney, liver, and joint synovia. Mumps virus causes necrosis of infected cells and is associated with a lymphocytic inflammatory infiltrate. Salivary gland ducts are lined with necrotic epithelium, and the interstitium is infiltrated with lymphocytes. Swelling of tissue within the testes may result in focal ischemic infarcts. The cerebrospinal fluid (CSF) frequently contains a mononuclear pleocytosis, even in individual without clinical signs of meningitis.

Virus can be isolated from saliva, blood, urine and CSF. Virus can be isolated from saliva 6 days before and up to 9 days appearance of the parotid or salivary gland swelling. This is the period of infectivity. Virus has been isolated from urine from first to 14th day after the onset of salivary gland swelling. Secondary attack rate is 80%. First trimester mumps is associated with increased fetal mortality.

## **CLINICAL FEATURES (FIG. 1)**

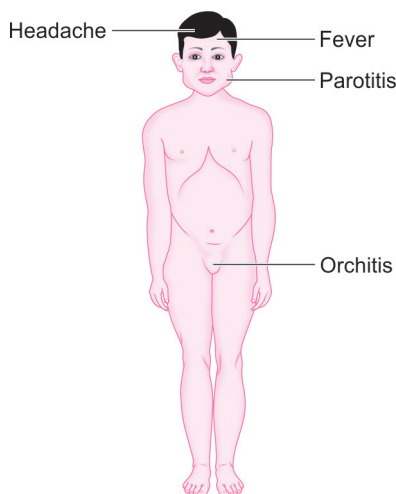
The incubation period ranges from 14 to 24 days with the peak at 17–18 days. The prodromal symptoms may be manifested by fever, muscular pain, headache and malaise.

A patient with mumps rarely has severe systemic manifestations. Body temperature is typically only moderately elevated for 3–4 days. Symptoms such as abdominal discomfort, anorexia, and headache may precede parotid gland involvement by 1–2 days.

The onset is usually characterized by pain and swelling in one or both parotid glands. Edema of skin and soft tissue extend further and obscure the limit of the glandular swelling. Parotid swelling, however, may be the first sign of illness. It is better seen than felt. It reaches the maximum size by 1–3 days. Swollen tissues push the earlobe upward and outward. Angle of the mandible is not visible. Swelling usually subsides by 3–7 days. Swelling may last 7–10 days and be observed on one or both sides of the face. The submandibular glands may also swell either in addition to the parotid or sometimes in the absence of parotid involvement. Presternal edema is sometimes present. There will be redness and swelling at the orifice of the Wharton's duct. The orifice of the Stensen's duct may show signs of inflammation.

### **ESSENTIAL DIAGNOSTIC POINTS**

- No prior mumps immunization
- Parotid gland swelling
- Aseptic meningitis with or without parotitis
- Orchitis



**Fig. 1:** Clinical features.

Some patients with mumps complain of abdominal pain, which could represent involvement of the pancreas or, in the female, the ovaries. Serum amylase is usually elevated during mumps infection, and vomiting can occur.

Complications from mumps disease are more common among adults than children. The most feared complication of mumps in males is orchitis. Although orchitis has been reported to occur in persons as young as 3 years of age, it is seen most frequently in post-pubertal males, with the highest incidence in those 15–29 years of age. Orchitis is estimated to occur in 14–35% of males with mumps disease. The onset of orchitis is usually heralded by fever toward the 1st week of illness. Severe pain, swelling and tenderness, which may persist for weeks, are common. Involvement is most often unilateral, but bilateral involvement has been reported. Testicular atrophy may occur after mumps orchitis unilateral atrophy does not result in sterility, but sterility may occur if the patient has bilateral orchitis. The development of malignancy in mumps-affected testes has been reported.

Other glands may also be occasionally involved with mumps disease. Mastitis is estimated to occur in 31% of females older than 15 who are infected with mumps virus. Findings of oophoritis include emesis, fever, and lower abdominal pain. Involvement of the thyroid gland and the development of diabetes mellitus have both been reported to occur after the onset of mumps.

Mumps virus is neurotropic, and more than 50% of patients with mumps disease have CSF pleocytosis. However, less than 10% have findings typical of aseptic meningitis. Mumps meningitis can occur in the absence of parotid involvement. CSF findings show predominantly lymphocytic cells, with counts usually <500 cells/ $\mu$ L; CSF glucose is typically normal to slightly low, with CSF protein normal to slightly high. Evidence of encephalitis occurs rarely in mumps disease.

Other manifestations include aseptic meningitis, encephalitis, auditory nerve damage, leading to deafness, cerebellar ataxia-facial neuritis, transverse myelitis and Guillain-Barré syndrome.

An association has been reported between mumps virus infection in the first trimester of pregnancy and an increased rate of fetal demise/spontaneous abortion. There is no convincing evidence, however, that mumps virus, which can cross the placenta, produces congenital malformations. Mumps virus has been isolated from breast milk. Deafness is a known complication associated with mumps disease, occurring in 1 in 20,000 reported cases. Permanent hearing

impairment is most often unilateral with higher tone frequency loss, the most severe. Onset of hearing loss is typically sudden and is not related to CNS involvement. Mumps infected mothers also prone to have low birth weight babies. Recently, intrauterine mumps is associated with endocardial fibroelastosis.

#### GENERAL FEATURES

- Nausea
- Malaise
- Loss of appetite
- Submaxillary and sublingual glands are enlarged
- Encephalitis

#### DIAGNOSIS

When mumps was highly prevalent, the diagnosis could be made on the basis of a history of exposure to mumps infection, an appropriate incubation period, and development of typical clinical findings. Confirmation of the presence of parotitis could be made with demonstration of an elevated serum amylase value. Leukopenia with a relative lymphocytosis was a common finding. Enzyme immunoassay (EIA) of immunoglobulin G (IgG) and immunoglobulin M (IgM) levels is commonly used. Mumps virus can be isolated in cell culture inoculated with buccal swab, throat washing, saliva or CSF, or urine during the acute illness.

Serologic testing is usually a more convenient and available mode of diagnosis. A significant increase in serum mumps immunoglobulin G antibody between acute and convalescent serum specimens as detected by complement fixation, neutralization, hemagglutination, or enzyme immunoassay tests establishes the diagnosis. These are rarely done, but it is possible to identify infection acutely by detecting antibodies to the “S” antigen by complement fixation antibody titers, which rise in 1st week of illness, and “V” antigen by complement fixation antibody titers that follow with a rise several weeks later, and may persist at low levels for years. Neutralizing and hemagglutination inhibiting antibodies appear during convalescence.

Confirmation of the diagnosis of mumps infection is accomplished by: (1) isolation of the virus in culture; (2) detection of mumps virus nucleic acid by reverse transcriptase polymerase chain reaction (RT-PCR) from either saliva or CSF; (3) detection of mumps-specific IgM antibodies or (4) demonstration of a significant mumps serum IgG antibody titer rise, quantitatively or semi-quantitatively, between acute and convalescent (2 or more weeks apart) serologic assays.

Reverse transcription polymerase chain reaction (RT-PCR) is becoming increasingly more available, and consequently, culture is now performed less frequently. A negative IgM test in a previously immunized individual does not eliminate the diagnosis of mumps, because an IgM response may be absent. In addition, again in a previously immunized patient, an IgG titer rise may be blunted by the presence of preexisting antibody. Viral excretion in saliva from a previously immunized person with possible mumps may also be shortened in duration.

## DIFFERENTIAL DIAGNOSIS

Human immunodeficiency virus (HIV), influenza, *Cytomegalovirus* (CMV), coxsackie virus, suppurative parotitis, recurrent parotitis, lymphadenitis, and calculus in stenosis duct.

### LABORATORY SALIENT FINDINGS

- CSF analysis shows lymphocytosis
- Viral culture of saliva throat, urine, spinal fluid
- Enzyme-linked immunosorbent assay (ELISA)
- Complement fixing antibody to the antigen

## COMPLICATIONS

- Orchitis, thyroiditis
- Epididymitis
- Pancreatitis
- Oophoritis
- Nephritis
- Meningoencephalomyelitis

## TREATMENT

There is no specific treatment. Antipyretics, bed rest and diet are recommended. Paracetamol and aspirin are given to relieve pain. Warm saline mouthwash is advised. Orchitis is treated with local support and steroids. Steroids relieve pain and swelling of orchitis and arthritis quickly.

## PREVENTION

The control of mumps is difficult because the disease is infectious before a diagnosis can be made. The long and variable incubation period and occurrence of subclinical cases make the control of the spread difficult. However, the cases should be isolated till the clinical manifestations subside. Contacts should be kept under surveillance.

It is given as part of the MMR two-dose vaccine schedule, at 12–15 months of age for the 1st dose and 4–6 years of age for the 2nd dose. If not given at 4–6 years, the 2nd dose should be given before children enter puberty. Antibody develops in 94% (range: 89–97%) of vaccinees after one dose. Antibody levels achieved following vaccination are lower than following natural infection.

## PROGNOSIS

The outcome of mumps is nearly always excellent, even when the disease is complicated by encephalitis, although fatal cases from CNS involvement or myocarditis have been reported.

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## PRESENTING COMPLAINTS

A 4-year-old boy was presented with the complaints of:

- Fever since 5 days
- Limping of the right leg since 3 days

## History of Presenting Complaints

A 4-year-old boy came to the pediatric outpatient department with a history of fever and limping. The boy was doing well apparently. He developed pain in the right leg at the ankle joint. This was there since last 3 days. There was so much pain that he started to limp while walking. His mother has noticed that there was a swelling and localized area was more warmer. There was decreased movement of the involved leg. This was associated with the fever. Fever was of moderate to high degree and was present since 3 days. The fever was sometimes associated with chills and rigor.

### CASE AT A GLANCE

#### Basic Findings

Height	: 99 cm (50th centile)
Weight	: 16 kg (80th centile)
Temperature	: 39°C
Pulse rate	: 120 per minute
Respiratory rate	: 30 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Limping
- Fever
- Swelling at the right leg

##### Examination

- Toxic
- Febrile
- Right inguinal lymphadenitis
- Tenderness at the right leg

##### Investigation

- TLC: Raised
- ESR: Raised
- X-ray: Moth-eaten destruction

## Past History of the Patient

The boy was the second sibling of nonconsanguineous marriage. He was born at full term by normal delivery. There was no significant postnatal event. He started taking breast milk. He was on exclusively breast milk for the first 4 months, later weaning was started and child was on family food by 16 months. His developmental milestones were normal. He was immunized completely apart from regular respiratory tract infection, there was no major health problem. His elder sibling was sister. She was doing well with the health.

## EXAMINATION

On examination, the child was moderately built and nourished. Child was looking toxic. He was not keeping down his right leg. His anthropometric measurements included, the height was 99 cm (50th centile), and the weight was 16 kg (80th centile). He was febrile, i.e., 39°C. His pulse rate was 120 per minute. The respiratory rate was 30 per minute. The blood pressure recorded was 70/50 mm Hg. There was no pallor, no edema. Right-sided inguinal lymphadenitis was present. There was tenderness at the lower end of the leg. There was swelling over the lower end of the tibia. All the systemic examinations were normal.

## INVESTIGATIONS

Hemoglobin	: 12 g/dL
TLC	: 15,000 cells/cu mm
DLC	: $P_{78} L_{22}$
ESR	: 58 mm in the 1st hour
CRP	: 1,260 µg/L (Normal range: 67–1,000 µg/L)

Blood culture and sensitivity	: Sterile
Mantoux test	: Negative
X-ray chest	: Normal
MRI	: Normal
X-ray of the long bone	: Moth-eaten destruction, cortex is thickened and lamellated

## DISCUSSION

Osteomyelitis is an infectious process that usually starts in the spongy or medullary bone and then extends to involve compact or cortical bone. The lower extremities are most often affected, and there is commonly a history of trauma.

Osteomyelitis may occur as a result of direct invasion from the outside through a penetrating wound or open fracture, but hematogenous spread of infection (e.g., pyoderma or upper respiratory tract infection) from other infected areas is much more common.

There is frequently a history of some, type of minor blunt trauma illness such as an upper respiratory tract infection. Other risk factors for acute hematogenous osteomyelitis (AHO) include immunodeficiency states, sickle cell anemia, and indwelling vascular catheters.

The most common infecting organism is *Staphylococcus aureus*, which has a tendency to infect the metaphysis of growing bones. Anatomically, circulation in the long bones is such that the arterial supply to the metaphysis just below the growth plate is by end arteries, which turn sharply to end in venous sinusoids, causing a relative stasis.

In the infant under age 1 year, there is direct vascular communication with the epiphysis across the growth plate, so that direct spread may occur from the metaphysis to the epiphysis and subsequently into the joint.

In the older child, the growth plate provides an effective barrier and the epiphysis is usually not involved, although the infection spreads retrograde from the metaphysis into the diaphysis and, by rupture through the cortical bone, down along the diaphysis beneath the periosteum.

## Exogenous Osteomyelitis

To avoid osteomyelitis by direct extension, all wounds must be carefully examined and cleaned. Osteomyelitis is a common occurrence from pressure sores in anesthetic areas, such as in patients with spina bifida.

Cultures of the wound made at the time of exploration and debridement may be useful if signs of infection develop subsequently. Copious irrigation is necessary, and all nonviable skin, subcutaneous tissue, fascia, and muscle must be excised. In extensive or contaminated wounds, antibiotic coverage is indicated.

Contaminated wounds should be left open and secondary closure performed 3–5 days later.

If at the time of delayed closure further necrotic tissue is present, it should be excised. Leaving the wound open allows the infection to stay at the surface rather than extend inward to the bone.

Puncture wounds are especially liable to lead to osteomyelitis and should be carefully debrided if there is suspicion that they are deeper than the subcutaneous fat. The risk is greatest if the physis or growth plate of the bone is involved or synovium is damaged.

Bacteria are the most common pathogens in acute skeletal infections. *Staphylococcus aureus* is the most common infecting organism in osteomyelitis among all age groups, including newborns.

Group B *Streptococcus* (GBS) and gram-negative enteric bacilli (*Escherichia coli*, are also prominent pathogens in neonates; group A *Streptococcus* constitutes <10% of all cases. After 6 years of age, most cases of osteomyelitis are caused by *S. aureus*, *Streptococcus*, or *Pseudomonas aeruginosa*. *P. aeruginosa* from the foam padding of the shoe into bone or cartilage, which develops as osteochondritis. *Salmonella* species and *S. aureus* are the two most common causes of osteomyelitis in children with sickle cell anemia. *Streptococcus pneumoniae* most commonly causes osteomyelitis in children younger than 24 months of age and in children with sickle cell anemia, but its frequency has declined because of pneumococcal conjugate vaccines. *Bartonella henselae* can cause osteomyelitis of any bone, but especially in pelvic and vertebral bones.

*Streptococcus agalactiae* (GBS) and enteric gram-negative organisms occur almost exclusively in neonates. *Salmonella* is most commonly isolated in patients with acute hematogenous osteomyelitis, who have sickle cell anemia, although it can occasionally occur in normal hosts. *Haemophilus influenzae* type b, an important pathogen in older series, is now rarely seen in countries that routinely use the *H. influenzae* type b conjugate vaccine. Less common organisms causing osteomyelitis include *Bartonella henselae* (the cause of cat scratch disease), *Brucella*, and *Mycobacterium tuberculosis*.

Causes of nonhematogenous osteomyelitis in children include *Pseudomonas* osteochondritis, usually resulting from puncture wounds to the feet through sneakers, and anaerobic, gram-negative, and polymicrobial infections that occur after puncture wounds or open fractures.

Infections and other conditions, which may predispose may include impetigo, furunculosis,

infected lesion of the varicella, infected burns and direct trauma.

The fungal infection is caused by *Candida*. Infection with atypical mycobacteria can occur with the penetrating injury.

## Hematogenous Osteomyelitis

Hematogenous osteomyelitis is usually caused by pyogenic bacteria; 85% of cases are due to staphylococci. Streptococci are a less common cause of osteomyelitis. *Pseudomonas* organisms are common in cases of nail puncture wounds. Children with sickle cell anemia are especially prone to osteomyelitis caused by *Salmonella*.

It generally begins as a hematogenous abscess at metaphysis.

Abscess ruptures subperiosteally, spreading along the shaft of the bone penetrating the marrow cavity. The periosteum may separate and form shell of the new bones. The pieces of the dead bone is called sequestrum. The new bone formed is called involucrum.

## PATHOGENESIS

The unique anatomy and circulation of the ends of long bones results in the predilection for localization of blood-borne bacteria. In the metaphysis, nutrient arteries branch into non-anastomosing capillaries under the physis, which make a sharp loop before entering venous sinusoids draining into the marrow. Blood flow in this area is thought to be “sluggish”, predisposing to bacterial invasion.

Once a bacterial focus is established, phagocytes migrate to the site and produce an inflammatory exudate (metaphyseal abscess). The generation of proteolytic enzymes, toxic oxygen radicals, and cytokines results in decreased oxygen tension, decreased pH, osteolysis, and tissue destruction. As the inflammatory exudate progresses, pressure increases spread through the porous metaphyseal space via the Haversian system and Volkmann canals into the subperiosteal space. Purulence beneath the periosteum may lift the periosteal membrane of the bony surface, further impairing blood supply to the cortex and metaphysis.

In newborns and young infants, transphyseal blood vessels connect the metaphysis and epiphysis, so it is common for pus from the metaphysis to enter the joint space. This extension through the physis has the potential to result in abnormal growth and bone or joint deformity.

During the latter part of the 1st year of life, the physis forms, obliterating the transphyseal blood vessels. Joint involvement, once the physis forms, can occur in joints where the metaphysis is intra-articular (hip, ankle, shoulder, and elbow), and subperiosteal pus ruptures into joint space.

In later childhood, the periosteum becomes more adherent, favoring pus to decompress through the periosteum. Once the growth plate closes in late adolescence, hematogenous osteomyelitis more often begins in the diaphysis and can spread to the entire intramedullary canal. Septic arthritis contiguous with a site of osteomyelitis is also seen in older children with *S. aureus* osteomyelitis, which may be related to simultaneous hematogenous inoculation of bone and joint space.

In the metaphysis, there are tiny vascular loops in which blood flow is sluggish. Oral oxygen tension is low. Rupture of sinus of the vessels occurs as a result of trauma. It provides favorable environment for the multiplication of the bacteria.

## CLINICAL FEATURES (FIG. 1)

Osteomyelitis may occur at any age. But it occurs more commonly between 3 and 12 years. It is more common among boys.

The earliest signs of osteomyelitis in infants may be failure to move the affected extremity (pseudoparalysis), pain on passive movement, or both. Older children typically present with fever, pain at the site of infection, and refusal to use the affected extremity, which usually translates to limping or refusal to bear weight because lower extremity bones are affected more frequently.

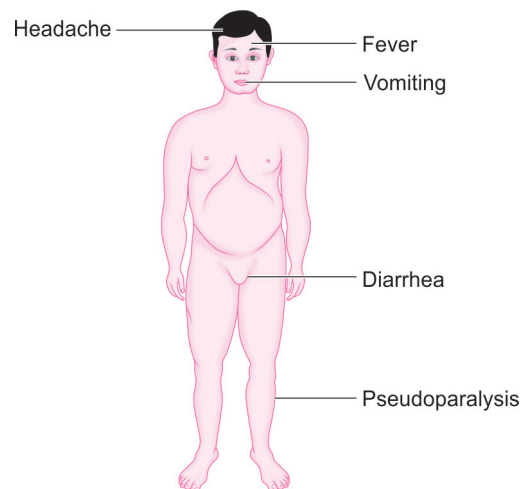


Fig. 1: Clinical features.

There can be intense tenderness over the metaphysis of the bone on palpation, and muscles of the adjacent joint are frequently in spasm.

In infants, the manifestations of osteomyelitis may be subtle, presenting as irritability, diarrhea, or failure to feed properly; the temperature may be normal or slightly low; and the white blood count may be normal or only slightly elevated.

In older children, the manifestations are more striking, with severe local tenderness and pain, often high fever, rapid pulse, and elevated white blood count and sedimentation rate. Osteomyelitis of a lower extremity often occurs around the knee joint in children aged 7–10 years. Tenderness is most marked over the metaphysis of the bone where the process has its origin. The child may limp or refuse to bear weight.

Usually only a single site of bone or joint is involved, although multiple sites of osteomyelitis may be noted in up to 20% of children with *S. aureus* infections. In neonates, two or more bones are involved in almost half of the cases. Children with subacute symptoms and focal findings in the metaphyseal area (usually of tibia) might have a Brodie abscess, with radiographic lucency and surrounding reactive bone. Typically, the contents of Brodie abscesses are sterile.

The joint is held in a position of comfort, usually mild flexion, but to a lesser degree than with septic arthritis. Soft tissue changes of swelling, erythema, and heat are generally late findings in osteomyelitis. After several days, a sympathetic sterile effusion may form in a nearby joint, presenting a problem in differentiation from septic arthritis. It is imperative for the evaluating physician to remember that any infant or child with fever and failure to bear weight or use an extremity needs to be carefully evaluated for potential musculoskeletal infection.

Although essentially any bone can be involved, long bones are most often involved in acute hematogenous osteomyelitis in children. As noted, the majority of infections occur in the lower extremities, and the most common sites of involvement are the distal femoral and proximal femoral metaphysis. Next in frequency are the proximal femoral metaphysis and distal metaphysis of the radius and humerus. The femur and tibia are equally affected. There will be abrupt illness, fever and systemic sign of toxicity. There may be associated swelling erythema, tenderness of the involved part. There will be marked tenderness over the involved bone. Hematogenous osteomyelitis of the cervical vertebrae may be

manifested as torticollis. Infection in flat bones occurs most often in the pelvis and calcaneus, both of which can present challenges in diagnosis.

#### GENERAL FEATURES

- Fever
- Pain
- Redness and swelling of the skin and soft tissue
- Nausea

#### DIAGNOSIS

The diagnosis of osteomyelitis is clinical, blood cultures should be performed in all suspected cases.

There are no specific laboratory tests for osteomyelitis. The white blood cell count and differential, erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP) are generally elevated in children with bone infections but are nonspecific and not helpful in distinguishing between skeletal infection and other inflammatory processes. Monitoring elevated ESR and CRP may be of value in assessing response to therapy or identifying complications.

Blood cultures are often positive early. The most significant test in infancy is the aspiration of pus when suspicion arises because of lack of movement in a painful extremity. It is useful to needle the bone in the area of suspected infection and aspirate any fluid present. This fluid should be stained for organisms and cultured. Even edema fluid may be useful for determining the causative organism. The white blood cell count is usually elevated, as is the sedimentation rate.

#### LABORATORY SALIENT FINDINGS

- Positive blood culture
- Elevated WBCs, raised ESR
- X-ray: Nonspecific local swelling, elevation of periosteum, formation of new bone, dead bone fragments
- MRI: edema in early, soft tissue thickening

#### Radiograph

Nonspecific local swelling is the first X-ray finding. This is followed by elevation of the periosteum, with formation of new bone from the cambium layer of the periosteum occurring after 3–6 days. As the infection becomes chronic, areas of cortical bone are isolated by pus spreading down the medullary canal, causing rarefaction and demineralization of the bone. Such isolated pieces of cortex become ischemic and form sequestra (dead bone fragments). These X-ray findings are late but specific.

**ESSENTIAL DIAGNOSTIC POINTS**

- It is an infectious process
- It affects metaphysis
- Pseudoparalysis
- Toxic look
- Leukocytosis
- Focus of infection in hematogenous type

## Computed Tomography/ Magnetic Resonance Imaging

Computed tomography (CT) can demonstrate osseous and soft-tissue abnormalities and is ideal for detecting gas in soft tissues. CT is a valuable imaging modality. Magnetic resonance imaging (MRI) is more sensitive than CT or radionuclide imaging in acute osteomyelitis and is the best radiographic imaging technique for identifying abscesses and for differentiating between bone and soft-tissue infection. MRI provides precise anatomic detail of subperiosteal pus and accumulation of purulent debris in the bone marrow and metaphysis for possible surgical intervention. In acute osteomyelitis, purulent debris and edema appear dark, with decreased signal intensity. MRI can also demonstrate a contiguous or isolated septic arthritis, pyomyositis, or venous thrombosis.

## Radionuclide Studies

Radionuclide imaging can be valuable in suspected bone infections especially early in the course of infection and/or if multiple foci are suspected or an unusual site is suspected, as in the pelvis. Technetium-99 methylene diphosphonate ( $^{99m}\text{Tc}$ ), which accumulates in areas of increased bone turnover, is the preferred agent for radionuclide bone imaging (3-phase bone scan).

## Bone Aspiration and Biopsy

Bone cultures are positive in 38–91% of cases and confirm the diagnosis. Blood cultures are also very useful, demonstrating the organism in 30–76% of cases. The highest diagnostic yield occurs when both blood and bone specimens are submitted for culture. Recovery of organisms is enhanced by inoculating bone aspirates into blood culture bottles. This is particularly important when fastidious organisms (e.g., *Kingella*) are suspected, which may require up to a week of incubation before growth is evident. Alternatively, bone aspirates can be submitted for PCR testing when trying to establish a diagnosis in culture-negative osteomyelitis. In multiple studies, PCR testing has been shown to be particularly useful for the

diagnosis of *Kingella* acute hematogenous osteomyelitis, but when available, can also be used to identify other organisms in cases where conventional cultures are negative.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of osteomyelitis includes cellulitis, septic arthritis, Pyomyositis, malignancy, collagen vascular disease, and trauma. In differentiating cellulitis from bone infection, tenderness disproportionate to physical findings suggests osteomyelitis. Septic arthritis may be differentiated from osteomyelitis by its more discrete joint findings and its greater degree of joint immobility, in addition to a lack of metaphyseal tenderness. History, physical examination, clinical scenario, and radiologic studies are helpful in differentiating skeletal infection from other diagnoses. Recovery of the causative organism is best obtained by biopsy or aspiration, which not only establishes the diagnosis but also facilitates susceptibility testing and rules out other pathologic processes.

## TREATMENT

### Specific Measures

Optimal treatment of skeletal infections requires collaborative efforts of pediatricians, orthopedic surgeons, and radiologists. Obtaining material for culture (blood, periosteal abscess, bone) before antibiotics are given is essential.

### Antibiotic Therapy

The empiric antibiotic therapy is based on the knowledge of likely organism with particular age group.

In the young infant, GBS and *S. aureus* are the major pathogens, but coverage of enteric gram-negatives must be included. An appropriate initial therapeutic regimen includes an anti-staphylococcal agent plus a third-generation cephalosporin, such as cefotaxime.

In neonates, an antistaphylococcal penicillin, such as nafcillin or oxacillin (150–200 mg/kg/24 h divided q12h IV), and a broad-spectrum cephalosporin, such as cefotaxime (150–225 mg/kg/24 h divided q8h IV), provide coverage for the methicillin-susceptible *S. aureus*, GBS, and gram-negative bacilli. If methicillin-resistant *Staphylococcus* is suspected, vancomycin is substituted for nafcillin.

If the neonate is a small premature infant or has a central vascular catheter, the possibility of nosocomial bacteria (gram-negative enteric,



*Pseudomonas*, or *Staphylococcus aureus*) or fungi (*Candida*) should be considered. In older infants and children, the principal pathogens are *S. aureus* and *Streptococcus*.

In children less than 4 years of age, a regimen providing coverage for *S. aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Kingella* should be used. An anti-staphylococcal agent plus a third-generation cephalosporin may provide appropriate coverage.

In infants and children, about 4–5 years, the main pathogen may be *S. aureus*, *Streptococcus* and *H. influenzae*. Then the third generation cephalosporins are used. Cefuroxime (100–150 mg/kg/24 h) in three divided doses, cefotaxime 150 mg/kg/day in three divided doses and ceftriaxone (50 mg/kg/24 h) given once daily. Antistaphylococcal antibiotics such as nafcillin (15 mg/kg/day) in four divided doses, or cephalothin 100–150 mg/kg/24 h in four divided doses.

A major factor influencing the selection of empirical therapy is the rate of methicillin resistance among community *S. aureus* isolates. If methicillin-resistant *S. aureus* (MRSA) accounts for >10% of community *S. aureus* isolates, including an antibiotic effective against MRSA in the initial empirical antibiotic regimen is suggested vancomycin (60 mg/kg/24 h divided q6hr IV) is the gold standard agent for treating invasive MRSA infections, especially when the child is critically ill. Clindamycin (40 mg/kg/24 h q8hr) is also recommended when the rate of clindamycin resistance is 5–10% among community *S. aureus* isolates, the child is not severely ill and bacteremia is not a concern or blood cultures are known to be negative. Cefazolin (100 mg/kg/24 h divided q8h IV) or nafcillin (150–200 mg/kg/24 h divided q6h) is the agent of choice for parenteral treatment of osteomyelitis caused by methicillin-susceptible *S. aureus*. Penicillin is first line therapy for treating osteomyelitis caused by susceptible strains of *Streptococcus pneumoniae* as well as all group A streptococci. Cefotaxime or ceftriaxone is recommended for pneumococcal isolates with resistance to penicillin and for most *Salmonella* sp.

In immunocompromised children or those with underlying medical conditions, broader-spectrum coverage may be appropriate. *Pseudomonas* is a consideration, and antipseudomonal agent may be part of the regimen.

For immunocompromised patients, combination therapy is usually initiated, such as with vancomycin and ceftazidime, or with piperacillin-tazobactam and aminoglycoside. *K. kingae* usually

responds to beta-lactam antibiotics including cefotaxime.

If possible, initiating treatment with a single agent is preferred. If cultures remain sterile, treatment should be continued based on the most common organism for the age group, usually *S. aureus*. If there is no response to treatment, less common organisms may be suspected, although there may be other causes as well (e.g., the common etiologic agent is resistant to the chosen antibiotic regimen or there are complications of the infection). In children under 1 year of age with negative cultures, *K. kingae* should strongly be considered.

After the initial period of intravenous antibiotic therapy for 5–7 days, patient should be treated adequately with oral antibiotics. Inadequate antibiotic therapy often leads to chronic disease and orthopedic deformity. Changing antibiotics from the intravenous route to oral administration when a patient's condition clearly has improved and the child is afebrile for 48–72 hours may be considered. For the oral antibiotic regimen with  $\beta$ -lactam drugs for susceptible staphylococcal or streptococcal infection, cephalexin (80–100 mg/kg/24 h q8h) or oral clindamycin (30–40 mg/kg/24 h q8h) can be used to complete therapy for children with clindamycin-susceptible MRSA or for patients who are seriously allergic or cannot tolerate  $\beta$ -lactam antibiotics. Surgical treatment involves surgical removal of sinus and debridement of sequestrum.

The usual recommended duration is 4–6 weeks, but depends on the cause and extent of infection as well as clinical and laboratory response. However, some newer studies have shown successful outcomes with 3 weeks of therapy. Each patient must be evaluated individually, taking into account the speed of clinical response, whether surgical debridement was done, normalization of CRP or ESR, and radiologic findings.

## General Measures

Splinting of the limb minimizes pain and decreases spread of the infection by lymphatic channels through the soft tissue. The splint should be removed periodically to allow active use of adjacent joints and prevent stiffening and muscle atrophy. In chronic osteomyelitis, splinting may be necessary to guard against fracture of the weakened bone.

## Surgical Measures

The need for open surgery in osteomyelitis depends on the extent of the pathologic process

in individual patients and likely somewhat on the virulence of the specific pathogen. In children who present early in the “cellulitic phase”, antibiotic therapy alone is usually sufficient for treatment. If pus is encountered during diagnostic aspiration, if a subperiosteal or intramedullary abscess is detected by ultrasound or MRI, or if a bone lesion is evident on plain films, surgical intervention may be warranted. Patients initiated on medical therapy who do not promptly improve should also be evaluated for surgical intervention.

Surgical drainage and debridement removes inflammatory products more rapidly than do host defense mechanisms, providing a more effective environment for antibiotic penetration and preventing further bone necrosis. Drainage of an abscess also reduces the inoculum of bacteria present. Any patient with a lytic lesion on plain films should have, in addition to cultures, the bone biopsy sent to pathology for histology and special stains to rule out other pathologic processes such as malignancy and to evaluate for unusual organisms such as fungi or acid-fast bacilli.

It is important that all devitalized soft tissue be removed and adequate exposure of the bone obtained to permit free drainage. Excessive amounts of bone should not be removed when draining acute osteomyelitis, because they may not be completely replaced by the normal healing process. Little damage is done by surgical drainage, but failure to drain the pus in acute cases may lead to more severe damage.

Treatment of chronic osteomyelitis consists of surgical removal of sinus tracts and sequestrum, if present. Antibiotic therapy is continued for several months or longer until clinical and radiographic findings suggest that healing has occurred. Monitoring the CRP or ESR is not helpful in most cases of chronic osteomyelitis.

Aspiration of the metaphysis for culture and Gram stain is the most useful diagnostic measure in any case of suspected osteomyelitis. In the first 24–72 hours, it may be possible to treat osteomyelitis by antibiotics alone. If frank pus is aspirated from the bone, however, surgical drainage is indicated. If the infection has not shown a dramatic response within 24 hours, surgical drainage is also indicated.

## COMPLICATIONS

### Chronic Osteomyelitis

The most common complication of AHO is chronic or recurrent osteomyelitis, which occurs in fewer than 5% of cases. Symptoms may include chronic or recurrent pain, swelling, erythema, or purulent discharge, and in some cases, sinus tract formation. Development of chronic osteomyelitis is more common following nonhematogenous osteomyelitis (e.g., following penetrating trauma). The hallmark of chronic osteomyelitis is bone necrosis. Therapy is primarily surgical with adjunctive long-term antibiotics. A bone biopsy should be obtained in chronic osteomyelitis for culture and for histopathology to exclude Langerhans cell histiocytosis, malignancy, and other causes.

### Other Complications and Outcomes

Pathologic fractures can occur but are rare. If the bone growth plate is involved, there is a risk of abnormal length of the affected bone. In general, the outcome of well-managed cases of acute osteomyelitis in pediatric patients is favorable.

## PROGNOSIS

When osteomyelitis is diagnosed in the early clinical stages and prompt antibiotic therapy is begun, the prognosis is excellent. If the process has been unattended for a week to 10 days, there is almost always some permanent loss of bone structure, as well as the possibility of growth abnormality.

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## PRESENTING COMPLAINTS

An 18-month-old boy was brought with the complaints of:

- Loose motion since 2 days
- Vomiting since 2 days
- Fever since 2 days
- Sudden onset of weakness in the left leg since 1 day

## History of Presenting Complaints

An 18-month-old boy was brought to pediatric outpatient department with history of sudden onset of weakness in left leg. Child was not able to stand as he is not able to put his left leg to the ground. Mother gave the history that his son was suffering from loose motion, vomiting and fever since last 2 days. He was getting treatment from general practitioner. As child had persistent vomiting, doctor had given an injection to control the vomiting. Mother noticed the development of weakness in the left leg after the injection.

### CASE AT A GLANCE

#### Basic Findings

Length	: 80 cm (50th centile)
Weight	: 10 kg (75th centile)
Temperature	: 38°C
Pulse rate	: 120 per minute
Respiratory rate	: 24 per minute
Blood pressure	: 60/40 mm Hg

#### Positive Findings

##### History

- Weakness in left leg
- Intramuscular weakness
- Crying
- Not immunized

##### Examination

- Febrile
- Weakness in left leg
- Paresthesia
- Moderate dehydration

##### Investigation

- Lumbar puncture: Pleocytosis and increased protein

Coincidentally the injection was given on the left gluteal region. Again she rushed back to the doctor and informed about the weakness. Later after examination he referred to pediatrician.

## Past History of the Patient

He was the only child of nonconsanguineous marriage. He was delivered at term by normal vaginal delivery. She never had any antenatal health check-up. There were no significant postnatal events. Baby was given breast milk immediately. Child was on exclusively breast milk for 6 months. Later child was given family food. Child was not given any immunization. His developmental milestones were normal.

## EXAMINATION

Boy was moderately built and nourished. He was irritable and was not allowing anybody to touch his left leg. He was not able to stand. The anthropometric measurements included, the weight was 10 kg (75th centile) and length was 80 cm (50th centile). He was febrile, heart rate was 120 per minute, respiratory rate was 24 per minute, and the blood pressure recorded was 60/40 mm Hg. Child was pale. There was no edema, no lymphadenopathy, no cyanosis and icterus.

There were signs of moderate dehydration. Central nervous system (CNS) revealed higher mental functions were normal. Anterior fontanelle is closed. No cranial nerve is involved. There were no meningeal signs. There was weakness and hypotonia in the left leg. Deep tendon reflexes were exaggerated. Child was not allowing anybody to touch his left leg. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 9,600 cells/cu mm
DC	: $P_{78} L_{18} E_2 M_2$
ESR	: 21 mm in 1st hour

Chest X-ray : NAD  
 Lumbar puncture : Pleocytosis cells 300 cells/cu mm  
 Proteins raised 100 mg/dL

## DISCUSSION

The combination of fever, asymmetric fluid paralysis, without sensory loss, and pleocytosis in cerebrospinal fluid (CSF) helps to arrive at diagnosis of poliomyelitis.

The polioviruses are non-enveloped and positive-stranded ribonucleic acid (RNA) viruses belonging to the family Picornaviridae, in the genus *Enterovirus* and consist of three antigenically distinct serotypes (types 1, 2, and 3). Polioviruses spread from the intestinal tract to CNS, where they cause aseptic meningitis and poliomyelitis, or polio. The polioviruses are extremely hardy and can retain infectivity for several days at room temperature. Poliovirus can survive for long periods for external environments. It can live in water for 4 months and in feces for 6 months. It is therefore well adapted for feco-oral transmission.

Man is the only reservoir and natural host of virus. Most infections are subclinical. It is the mild and subclinical infections that play a dominant role in the spread of infection. There are no chronic carriers. Poliovirus is excreted in the stools of the patient for 2 weeks before and 6–8 weeks after the onset of illness, sometimes as long as 3–4 months. Fecal contamination of the edible substance may occur either due to human association or through the flies. The virus is found in fecal and oropharyngeal secretion of the infected person.

The vulnerable age is between 6 months and 3 years. Several predisposing risk factors include fatigue, trauma, intramuscular infection, open procedure such as tonsillectomy done during the epidemics of polio and administration of alum containing DPT.

Poliomyelitis virus multiplies in the intestine. If there is no local immunity it travels to the required lymph nodes and reticuloendothelial structure. As a result, specific antibodies are produced in the blood and the gut. Antibodies act mainly at the site of extraneural proliferation of the virus.

Infants acquire immunity transplacentally from the mother. This immunity will last for 4–6 months of life and disappear at a variable rate. Active immunity after the natural infection lasts for life. Neutralizing antibodies develop within several days after the exposure often before the onset of illness. The early production of immunoglobulin G (IgG) antibodies is a result of replication of the virus

in the intestinal tract and deep lymphatic tissue. This occurs before the CNS is invaded. Local mucosal immunity, conferred mainly by IgA is an important defense against poliovirus.

## PATHOGENESIS

Polioviruses infect cells by adsorbing to the genetically determined poliovirus receptor. The virus penetrates the cell, is uncoated, and releases viral RNA. The RNA is translated to produce proteins responsible for replication of the RNA, shut of host cell protein synthesis, and synthesis of structural elements that compose the capsid. Mature virus particles are produced in 6–8 hours and are released into the environment by disruption of the cell.

The exact mechanism of entry into the CNS is not known. However, once entry is gained the virus may traverse neural pathways, and multiple sites within the CNS are often affected. The effect on motor and vegetative neurons is most striking and correlates with the clinical manifestations. Perineuronal inflammation, a mixed inflammatory reaction with both polymorphonuclear leukocytes and lymphocytes, is associated with extensive neuronal destruction. Petechial hemorrhages and considerable inflammatory edema also occur in areas of poliovirus infection.

Poliovirus selectively damages the motor and autonomic nervous system. Most commonly affected areas are the anterior horn cells of the spinal cord, vestibular and cranial nerve nuclei and vital centers in medulla and vermis and nuclei in the roof of cerebellum.

The poliovirus primarily infects motor neuron cells in the spinal cord (the anterior horn cells) and the medulla oblongata (the cranial nerve nuclei). Because of the overlap in muscle innervation by two to three adjacent segments of the spinal cord, clinical signs of weakness in the limbs develop when more than 50% of motor neurons are destroyed. In the medulla, less-extensive lesions cause paralysis, and involvement of the reticular formation that contains the vital centers controlling respiration and circulation may have a catastrophic outcome. Involvement of the intermediate and dorsal areas of the horn and the dorsal root ganglia in the spinal cord results in hyperesthesia and myalgias that are typical of acute poliomyelitis.

The neuropathy of poliomyelitis is due to direct cellular destruction. Neurological damage may include chromatolysis of Nissl substance in the cytoplasm. This is followed by changes in the nuclei and pericellular infiltration. The process

is reversible till this stage. If neurons undergo necrosis, the process becomes irreversible.

Secondary damage may be due to immunological mechanism. In poliomyelitis, the neural lesions occur in the roof and vermis of the cerebellum, the substantia nigra, and occasionally, the red nucleus in the pons; there may be variable involvement of thalamic, hypothalamic, and pallidal nuclei and the motor cortex.

Apart from the histopathology of the CNS, inflammatory changes occur generally in the reticuloendothelial system. Inflammatory edema and sparse lymphocytic infiltration are prominently associated with hyperplastic lymphocytic follicles.

Infants acquire immunity transplacentally from their mothers. Transplacental immunity disappears at a variable rate during the first 4–6 months of life. Active immunity after natural infection is probably lifelong but protects against the infecting serotype only; infections with other serotypes are possible. Poliovirus neutralizing antibodies develop within several days after exposure as a result of replication of the virus in the M cells in the intestinal tract and deep lymphatic tissues. This early production of circulating IgG antibodies protects against CNS invasion. Local (mucosal) immunity, conferred mainly by secretory IgA, is an important defense against subsequent reinfection of the gastrointestinal tract.

#### ESSENTIAL DIAGNOSTIC POINTS

- Headache, fever, and muscle weakness
- Asymmetric flaccid paralysis
- Muscle tenderness and hyperesthesia late atrophy
- Aseptic meningitis
- Inadequate immunization
- Underlying immune deficiency

### CLINICAL FEATURES (FIG. 1)

#### Inapparent Infections

This includes approximately 91–96%. There will not be presenting complaints. Diagnosis is done by isolation of virus and rising antibody titers.

#### Abortive Poliomyelitis

- Fever
- Anorexia and nausea
- Abdominal pain
- Constipation
- Loose motion
- Sore throat

#### Nonparalytic Poliomyelitis

- Headache
- Fleeting paralysis of the bladder

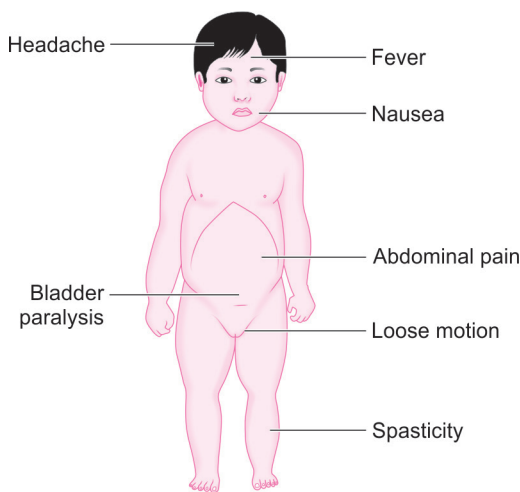


Fig. 1: Clinical features.

- First phase—minor
- Second phase—CNS
- Nuchal rigidity
- Spinal rigidity
- Tripod sign
- Kiss-knee sign
- Head drop
- Reflexes are active

#### Paralytic Poliomyelitis

- Bladder paralysis
- Bowel atony
- Pain, flaccid paralysis
- Spasticity
- Nuchal and spinal rigidity
- Respiratory and cardiac arrhythmias
- Blood pressure and vasomotor changes
- Spotty paralysis
- Spinal form—muscles of neck, abdomen, trunk, diaphragm
- Bulbar form—cranial nerves, vital centers
- Encephalitic form—irritability, disorientation, drowsiness, and coarse tremors

#### GENERAL FEATURES

- Nuchal rigidity
- Spinal rigidity
- Tripod sign
- Head drop
- Kiss-knee sign
- Spotty paralysis

### DIAGNOSIS

The combination of fever, headache, neck and back pain, asymmetric flaccid paralysis without sensory



loss and pleocytosis gives diagnosis of poliomyelitis. CSF during minor illness shows pleocytosis. Protein is normal, usually rises to between 50 and 100 mg/dL by the 2nd week of illness.

Characteristic clinical presentation of acute lower motor neuron type of asymmetrical paralysis of proximal limb muscles without any sensory involvement is highly suggestive of poliomyelitis. However, cases of acute flaccid paralysis cases should be investigated by sending a stool sample for isolation of virus.

## Stool Virus Isolation

Stool examination is recommended in every case of acute flaccid paralysis (AFP). Virus can be detected from onset to 8 or more weeks after paralysis; the highest probability of detection is during the first 2 weeks after onset of paralysis. Examination of the CSF (cell count, Gram stain, protein, and glucose) is useful in eliminating other conditions that cause AFP. Isolation of wild poliovirus from stool is the recommended method for laboratory confirmation of paralytic poliomyelitis. Two stool specimens are collected from each case for laboratory confirmation.

### LABORATORY SALIENT FINDINGS

- CSF analysis—lymphocytosis, mild elevated protein, normal protein
- Cell culture
- ELISA test

The World Health Organization (WHO) recommends that the laboratory diagnosis of poliomyelitis be confirmed by isolation and identification of poliovirus in the stool, with specific identification of wild-type and vaccine-type strains. In suspected cases of acute flaccid paralysis, two stool specimens should be collected 24–48 hours apart as soon as possible after the diagnosis of poliomyelitis is suspected. Poliovirus concentrations are high in the stool in the first week after the onset of paralysis, which is the optimal time for collection of stool specimens. Polioviruses may be isolated from 80–90% of specimens from acutely ill patients, whereas <20% of specimens from such patients may yield virus within 3–4 weeks after onset of paralysis. Because most children with spinal or bulbo-spinal poliomyelitis have constipation, rectal straws may be used to obtain specimens; ideally a minimum of 8–10 g of stool should be collected.

The CSF is often normal during the minor illness and typically contains a pleocytosis with 20–300 cells/dL, with CNS involvement. The cells

in the CSF may be polymorphonuclear early during the course of the disease but shift to mononuclear cells occurs soon afterwards. By the second week of major illness, the CSF cell count falls to near normal values. In contrast, the CSF protein content is normal or only slightly elevated at the outset of CNS disease but usually rises to 50–100 mg/dL by the second week of illness. In polioencephalitis, the CSF may remain normal or show minor changes. Serologic testing demonstrates seroconversion or a four-fold or greater increase in antibody titers from the acute phase of illness to 3–6 weeks later.

## DIFFERENTIAL DIAGNOSIS

- Guillain-Barré syndrome
- Aseptic meningitis
- Viral encephalitis
- Peripheral neuritis
- Encephalomyelitis

## TREATMENT

There is no specific antiviral treatment for poliomyelitis. The management is supportive and aimed at limiting progression of disease, preventing ensuing skeletal deformities, and preparing the child and family for the prolonged treatment required and for permanent disability, if this seems likely. Patients with the nonparalytic and mildly paralytic forms of poliomyelitis may be treated at home. All intramuscular injections and surgical procedures are contraindicated during the acute phase of the illness, especially in the first week of illness, because they might result in progression of disease.

The broad principles of management are to allay the fear, to minimize the skeletal deformities, to anticipate and meet the complications. Patients with nonparalytic and mildly paralytic forms may be treated at home.

## Abortive Poliomyelitis

Supportive treatment with analgesics, sedatives, an attractive diet, and bed rest until the child's temperature is normal for several days is usually sufficient. Avoidance of exertion for the ensuing 2 weeks is desirable, and careful neurological and musculoskeletal examinations should be performed 2 months later to detect any minor involvement.

## Nonparalytic Poliomyelitis

Treatment for the nonparalytic form is similar to that for the abortive form; in particular, relief is

indicated for the discomfort of muscle tightness and spasm of the neck, trunk, and extremities. Analgesics are more effective when they are combined with the application of hot packs for 15–30 minutes every 2–4 hours. Hot tub baths are sometimes useful. A firm bed is desirable and can be improvised at home by placing table leaves or a sheet of plywood beneath the mattress. A footboard or splint should be used to keep the feet at a right angle to the legs. Because muscular discomfort and spasm may continue for some weeks, even in the nonparalytic form, hot packs and gentle physical therapy may be necessary. Patients with nonparalytic poliomyelitis should also be carefully examined 2 months after apparent recovery to detect minor residual effects that might cause postural problems in later years.

### Paralytic Poliomyelitis

Most patients with the paralytic form of poliomyelitis require hospitalization with complete physical rest in a calm atmosphere for the first 2–3 weeks. Suitable body alignment is necessary for comfort and to avoid excessive skeletal deformity. A neutral position with the feet at right angles to the legs, the knees slightly flexed, and the hips and spine straight is achieved by use of boards, sandbags, and occasionally, light splint shells. The position should be changed every 3–6 hours.

Active and passive movements are indicated as soon as the pain has disappeared. Moist hot packs may relieve muscle pain and spasm. Opiates and sedatives are permissible only if no impairment of ventilation is present or impending. Constipation is common, and fecal impaction should be prevented.

When bladder paralysis occurs, a parasympathetic stimulant such as bethanechol may induce voiding in 15–30 minutes; some patients show no response to this agent, and others respond with nausea, vomiting, and palpitations. Bladder paresis rarely lasts more than a few days. If bethanechol fails, manual compression of the bladder and the psychological effect of running water should be tried. If catheterization must be performed, care must be taken to prevent urinary tract infections.

A proper diet and a relatively high fluid intake should be started at once unless the patient is vomiting. Additional salt should be provided if the environmental temperature is high or if the application of hot packs induces sweating. Anorexia is common initially. Adequate dietary and fluid intake can be maintained by placement of a central

venous catheter. An orthopedist and a physiotherapist should see patients as early in the course of the illness as possible and should assume responsibility for their care before fixed deformities develop.

The management of pure bulbar poliomyelitis consists of maintaining the airway and avoiding all risk of inhalation of saliva, food, and vomitus. Gravity drainage of accumulated secretions is favored by using the head-low (foot of bed elevated 20–25°) prone position with the face to one side. Patients may require tracheostomy because of vocal cord paralysis or constriction of the hypopharynx; most patients who recover have little residual impairment, although some exhibit mild dysphagia and occasional vocal fatigue with slurring of speech.

Patients with weakness of the muscles of respiration or swallowing should be nursed in a lateral or semiprone position. Aspirators with rigid or semirigid tips are preferred for direct oral and pharyngeal aspiration, and soft, flexible catheters may be used for nasopharyngeal aspiration.

Fluid and electrolyte equilibrium is best maintained by intravenous infusion because of tube or oral feeding in the first few days may incite vomiting. In addition to close observation for respiratory insufficiency, the blood pressure should be measure at least twice daily because hypertension is not uncommon and occasionally leads to hypertensive encephalopathy.

Impaired ventilation must be recognized early; mounting anxiety, restlessness, and fatigue are early indications for presumptive intervention. Tracheostomy is indicated for some patients with pure bulbar poliomyelitis, spinal respiratory muscle paralysis, or bulbospinal paralysis because such patients are generally unable to cough, sometimes for many months. Mechanical respirators are often needed.

### COMPLICATIONS

Paralytic poliomyelitis may be associated with numerous complications. Acute gastric dilation may occur abruptly during the acute or convalescent stage, causing further respiratory embarrassment; immediate gastric aspiration and external application of ice bags are indicated. Melena severe enough to require transfusion may result from single or multiple superficial intestinal erosions; perforation is rare. Mild hypertension for days or weeks is common in the acute stage and probably related to lesions of the vasoregulatory centers in the medulla and especially to underventilation.

Dimness of vision, headache and a lightheaded feeling associated with hypertension should be regarded as premonitory of a frank convulsion. Acute pulmonary edema occurs occasionally, particularly in patients with arterial hypertension. Hypercalcemia occurs because of skeletal decalcification that begins soon after immobilization and results in hypercalciuria.

## PROGNOSIS

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In general, the more extensive the paralysis in the first 10 days of illness, the more severe is the ultimate disability. Unexpected improvement may appear soon after defervescence and again about

6 weeks after the onset. This time that corresponds to functional restoration of temporarily inactive neurons. The degree of functional recovery depends upon adequacy and promptness of the supportive treatment, proper body positioning, active motion, use of assertive devices, and psychological motivation of the patient.

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# Septic Arthritis

## PRESENTING COMPLAINTS

A 9-month-old boy was brought with the complaints of:

- Fever since 2 days
- Swelling in the right knee since 1 day
- Decreased movements since 1 day

## History of Presenting Complaints

A 9-month-old boy was brought to the pediatric outpatient department with history of sudden onset of fever, and child was crying when his leg was touched. He was apparently normal about 2 days back. Mother told that all of a sudden, his son became much irritable and started crying excessively. On careful observation, his mother found that there was swelling around right knee joint. He was not allowing anyone to touch his leg. Mother had noticed that there was little warm over the knee joint compared to the surrounding region. There was history of fever, moderate-to-high degree.

### CASE AT A GLANCE

#### Basic Findings

Length	: 70 cm (50th centile)
Weight	: 7.75 kg (40th centile)
Temperature	: 39°C
Pulse rate	: 116 per minute
Respiratory rate	: 28 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Sudden onset of fever
- Redness and pain in the right knee
- Limping
- Past history of upper respiratory tract infection (URTI)

##### Examination

- Arthritis at right knee
- Tenderness
- Crepitation at right base chest

##### Investigation

- TLC: Raised
- ESR: Raised
- CRP: Raised

Fever used to be more in the evening and night, used to be relieved by antipyretics to little extent.

## Past History of the Patient

The boy was the only and first sibling of noncon-sanguineous marriage. He was born at full term by normal vaginal delivery. The baby cried immediately after delivery. The birth weight of child was 3 kg. Child was on breast milk immediately after the delivery, weaning of food was started at the age of 4 months. His developmental milestones were normal. Before the development of this problem, he had upper respiratory tract infection (URTI) about 1 week back. He had received treatment for that. He had been completely immunized.

## EXAMINATION

On examination, the child was moderately built and nourished. He was looking toxic, irritable and crying excessively. Anthropometric measurements included, the length was 70 cm (50th centile) and the weight was 7.75 kg (40th centile). The head circumference was 40 cm. The child was febrile 39°C and toxic signs of mild dehydration were present. The pulse rate was 116 per minute and the respiratory rate was 28 per minute. The blood pressure recorded was 70/50 mm Hg.

He was looking pale. There was no edema and no icterus. The right inguinal lymph nodes were enlarged. There was swelling in and around the knee joint. There was limitation of the movements at knee joints. Erythema, tenderness and warmth were present. Respiratory system revealed the presence of the basal crepitation on both lungs. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 22,000 cells/cu mm
DLC	: P <sub>72</sub> L <sub>25</sub> E <sub>3</sub>
ESR	: 56 mm in the 1st hour
ASLO	: 200 Todd units
CRP	: 2200 µg/L (Normal range: 70–1800 µg/L)

Chest X-ray : Normal  
X-ray of the right knee : Normal

## DISCUSSION

The boy presented with sudden onset of pain in knee joint which was associated with raised erythrocyte sedimentation rate (ESR). Leukocytosis and raised C-reactive protein (CRP) point to the diagnosis of septic arthritis. It most commonly occurs during the first year of life. It frequently follows the infection of the skin and upper respiratory tract.

Septic arthritis is more common in young children. Half of all cases occur by 2 years of age and three-fourths of all cases occur by 5 years of age. Adolescents and neonates are at risk of gonococcal septic arthritis.

*Haemophilus influenzae* type b accounted for more than half of all cases of bacterial arthritis in infants and young children. Since the development of the conjugate vaccine, it is now a rare cause; *Staphylococcus aureus* is now the most common infection in all age groups.

In sexually active adolescents, *Gonococcus* is a common cause of septic arthritis and tenosynovitis, usually of small joints or as a monoarticular infection of a large joint (knee). *Neisseria meningitidis* can cause either a septic arthritis that occurs in the first few days of illness or a reactive arthritis that is typically seen several days after antibiotics have been initiated. Group B *Streptococcus* is an important cause of septic arthritis in neonates.

Fungal infections usually occur as part of multi-system disseminated disease; *Candida* arthritis can complicate systemic infection in neonates with or without indwelling vascular catheters. Primary viral infections of joints are rare, but arthritis accompanies many viral (parvovirus, mumps, rubella live vaccines) syndromes, suggesting an immune-mediated pathogenesis.

## PATHOGENESIS

Predisposing factors for the development of septic arthritis vary with age. For example, in neonates, the presence of indwelling catheters including those in the umbilical vessels increases the risk, whereas in older children, risk factors include underlying medical conditions such as immunodeficiencies, diabetes, juvenile idiopathic arthritis (JIA), and hemoglobinopathies.

The source of pyogenic arthritis varies according to the child's age. In the infant, pyogenic arthritis often develops by spread from adjacent osteomyelitis. In the older child, it presents an isolated infection, usually without bony involvement.

In teenagers with pyogenic arthritis, an underlying systemic disease is usually the cause, such as an obvious generalized infection or an organism (e.g., *Gonococcus*) that has an affinity for joints.

The anatomy of the synovial joint provides an environment conducive to bacterial infection. The synovial tissue lining the joint lacks a basement membrane and therefore secretes a transudate of serum. The rest of the joint surface is composed of a vascular cartilage. Bacteria enter the joint by hematogenous seeding, direct extension from an adjacent focus, or direct inoculation during a joint aspiration, arthrotomy, or trauma.

Initially, after bacterial invasion occurs, the synovial membrane swells and produces increased amounts of fluid, distending the joint. Its infection persists without treatment, pus accumulates in the area and destruction of cartilage follows. Subluxation or dislocation of the joint may result from increased intra-articular pressure occurring when the joint capsule is distended by purulent fluid. This increased pressure may compromise blood supply in certain areas. In the hip, this may lead to a vascular necrosis of the femoral head.

Bacteria are deposited in the subsynovial capillary vessel network, with the migration of the bacteria and blood products into the joint space. If the host's immune system is well prepared, the arthritis does not progress and process is aborted.

Septic arthritis primarily occurs as a result of hematogenous seeding of the synovial space. Less often, organisms enter the joint space by direct inoculation or extension from a contiguous focus. The synovial membrane has a rich vascular supply and lacks a basement membrane, providing an ideal environment for hematogenous seeding.

The presence of bacterial products (endotoxin or other toxins) within the joint space stimulates cytokine production (tumor necrosis factor- $\alpha$ , interleukin-1) within the joint, triggering an inflammatory cascade. The cytokines stimulate chemotaxis of neutrophils into the joint space, where proteolytic enzymes and elastases are released by neutrophils, damaging the cartilage.

Proteolytic enzymes released from the synovial cells and chondrocytes also contribute to destruction of cartilage and synovium. Bacterial hyaluronidase breaks down the hyaluronic acid in the synovial fluid, making the fluid less viscous and diminishing its ability to lubricate and protect the joint cartilage.

Damage to the cartilage can occur through increased friction, especially for weight-bearing joints. The increased pressure within the joint space from accumulation of purulent material



can compromise the vascular supply and induce pressure necrosis of the cartilage. Synovial and cartilage destruction results from a combination of proteolytic enzymes and mechanical factors.

Articular cortical degradation occurs because of depletion of collagen and proteoglycogen. Pus in the joint space increases intracapsular pressure with the resulting decrease in blood flow to the epiphyses. This can lead to irreversible ischemic damage if the pressure is not relieved promptly.

The initial effusion of the joint rapidly becomes purulent. An effusion of the joint may accompany osteomyelitis in the adjacent bone. A white cell count exceeding 100,000/mL in the joint fluid indicates a definite purulent infection. Generally, spread of infection is from the bone into the joint, but unattended pyogenic arthritis may also affect adjacent bone. The sedimentation rate is often above 50 mm/h.

Delayed or inadequate treatment of a septic joint can result in permanent joint damage with subsequent disability. Septic arthritis is most common in children less than 3 years of age. In most cases, a single, large joint is involved, usually in the lower extremity. As in osteomyelitis, males are affected more frequently. There may be a history of trauma or recent infection of the skin or upper respiratory tract.

## Causative Agents

As in osteomyelitis, etiologic agents of septic arthritis vary by age. *Staphylococcus aureus* (MSSA and MRSA) is the leading organism in all age groups neonates, and enteric gram-negative organisms are also important to consider and may be isolated from an affected joint as a consequence of an adjacent osteomyelitis. *Staphylococcus aureus*, *Streptococcus pyogenes* and *Kingella kingae* are the most prominent causative pathogens in children less than 4 years of age. *Haemophilus influenzae* type b, the most common organism this age group in the past, is rarely seen now in countries that routinely vaccinate against this agent. In children older than 4 years, *S. aureus* and *S. pyogenes* are the chief pathogens. *Klebsiella* is a gram-negative bacterium that occasionally causes pyarthrosis.

## CLINICAL FEATURES (FIG. 1)

The onset may be sudden with systemic symptoms and fever. Local swelling may appear with pain and muscular rigidity, erythema, tenderness, and warmth.

Children generally present acutely with a painful, erythematous, warm joint, and refusal to

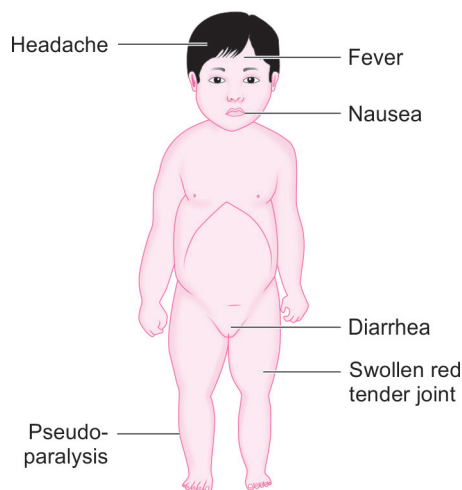


Fig. 1: Clinical features.

move or bear weight on the affected extremity. Fever, toxicity, and irritability are often accompanying features.

The joint is held in the position of most comfort, usually mild flexion when the hip is involved, erythema or joint swelling is generally not obvious but the affected hip is held in a position of flexion abduction, and external rotation. Young children may exhibit the phenomenon of “referred pain”, in which symptoms from an infected hip joint are referred to the ipsilateral knee. The differential diagnosis of septic arthritis includes cellulitis, bursitis, osteomyelitis (including patellar) with or without a sympathetic effusion, reactive arthritis, transient synovitis, arthritis associated with systemic disease such as juvenile idiopathic arthritis (JIA), or malignancy.

Most septic arthritis are monoarticular. The signs and symptoms of septic arthritis depend on the age of the patient. Early signs and symptoms may be subtle, particularly in neonates. Septic arthritis in neonates and young infants is often associated with adjacent osteomyelitis caused by transphyseal spread of infection, although osteomyelitis contiguous with an infected joint can be seen at any age.

Erythema and edema of the skin and soft tissue overlying the site of infection are seen earlier in septic arthritis than in osteomyelitis, because the bulging infected synovium is usually more superficial, whereas the metaphysis is located more deeply. Septic arthritis of the hip is an exception because of the deep location of the hip joint.

Joints of the lower extremity constitute 75% of all cases of septic arthritis. The elbow, wrist, and

shoulder joints are involved in approximately 25% of cases, and small joints are uncommonly infected. Suppurative infections of the hip, shoulder, elbow, and ankle in older infants and children may be associated with an adjacent osteomyelitis of the proximal femur, proximal humerus, proximal radius, and distal tibia because the metaphysis extends intra-articularly.

In older children, the signs may be striking, with fever, malaise, vomiting and restriction of motion. In infants, paralysis of the limb due to inflammatory neuritis may be evident. Infection of the hip joint in infants should be suspected if decreased abduction of the hip is present in an infant who is irritable or feeding poorly. A history of umbilical catheter treatment in the newborn nursery should alert the physician to the possibility of pyogenic arthritis of the hip.

#### ESSENTIAL DIAGNOSTIC POINTS

- Fever, malaise, and vomiting
- *Pseudoparalysis*: Paralysis of limb due to inflammatory neuritis
- Redness and swelling of the skin soft tissue
- *Leukocytosis*:  $>100,000/\text{dL}$ , indicate sepsis

Infants may have only pseudoparalysis of the extremity or apparent pain on movement of the joint. Most older infants and children have fever and localizing signs. Redness and swelling of the skin and soft tissue tend to be seen. The bulging, infected synovium is near the surface. Nonspecific systemic signs of infection such as nausea, vomiting, diarrhea, and headache are present in disseminated infection syndrome with multiple foci of infection or disease.

## DIAGNOSIS

Because of the risk of long-term orthopedic complications, septic arthritis is an orthopedic emergency. Joint aspiration is the most important component of the diagnostic evaluation. Other laboratory tests and radiologic studies are generally nonspecific, but findings may be useful to direct the evaluation.

Blood cultures should be performed in all cases of suspected septic arthritis. Aspiration of the joint fluid for Gram stain and culture when the history and physical findings indicate septic arthritis remains the definitive diagnostic technique and provides the optimal specimen for culture to confirm the diagnosis. Most large joint spaces are easy to aspirate, but the hip can pose technical problems; ultrasound guidance facilitates aspiration. Aspiration of joint pus provides the best specimen for bacteriologic culture of infection.

If *Gonococcus* is suspected, cervical, anal and throat cultures should also be obtained.

The white blood cell count and differential, ESR, and CRP are generally elevated in children with joint infections but are nonspecific and might not be helpful in distinguishing between infection and other inflammatory processes. Monitoring elevated ESR and CRP may be of value in assessing response to therapy or identifying complications. In one study of *S. aureus* septic arthritis, risk features for a site of osteomyelitis contiguous with septic arthritis included a CRP  $>10 \text{ mg/dL}$  at the time of admission, positive blood cultures or more than 2 days of fever following admission.

## Ultrasonography

Ultrasonography is particularly helpful in detecting joint effusion and fluid collection in the soft-tissue and subperiosteal regions. Ultrasonography is highly sensitive in detecting joint effusion, particularly for the hip joint, where plain radiographs are normal in more than 50% of cases of septic arthritis of the hip. Ultrasonography can serve as an aid in performing hip aspiration.

## Radionuclide Imaging

Radionuclide imaging compared to radiographs is more sensitive in providing supportive evidence of the diagnosis of septic arthritis; a scan may be positive within 2 days of the onset of symptoms.

## Radiography

Early distension of the joint capsule is nonspecific and difficult to measure by X-ray. In the infant with unrecognized pyogenic arthritis, dislocation of the joint may follow within a few days as a result of distension of the capsule by pus. Later changes include destruction of the joint space, resorption of epiphyseal cartilage, and erosion of the adjacent bone of the metaphysis. The bone scan shows increased flow and increased uptake about the joint.

#### LABORATORY SALIENT FINDINGS

- Increased leukocyte count
- Elevated ESR
- Arthrocentesis—Gram stain, antinuclear antibodies, elevated WBCs in joint fluid
- Blood culture and sensitivity
- Lactic acid concentration in joint fluid

## Joint Fluid Analysis

For patients in whom the diagnosis of septic arthritis is suspected, aspirating the affected

joint can be both diagnostic and in many cases therapeutic. Synovial fluid should be sent for Gram stain, aerobic cultures, and cell count with a leukocyte differential. Anaerobic, fungal, and acid-fast bacilli (AFB) cultures may be considered in some instances (e.g., immune compromised patients, penetrating injuries to the joint, post-procedure septic arthritis).

Joint fluid cultures are positive in 30–60% of cases. Inoculation of joint fluid into blood culture bottles increases the yield of cultures, particularly when the etiologic agent is fastidious such as, in the case of *K. kingae*. Leukocyte counts >50,000 cells/ $\mu$ L, with a predominance of segmented neutrophils, are suggestive of bacterial arthritis, even in the absence of a positive culture. However, it should be recognized that white blood cells (WBCs) in infected joint fluid can vary widely, ranging from 2,000 to 300,000/ $\mu$ L. Synovial fluid glucose and protein may be measured but are nonspecific.

Lactic acid concentration within the joint fluid is a reliable method for establishing a diagnosis of septic arthritis. In patients with septic arthritis, the mean lactic acid concentration in synovial fluid is 11.6 mmol/L (normal is 2.3 mmol/L).

#### GENERAL FEATURES

- Toxic
- Fever
- Dehydration

### DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes deep cellulitis, fungal arthritis, acute rheumatic fever, rheumatoid arthritis, toxic synovitis, traumatic arthritis, and Henoch-Schönlein purpura (HSP).

### TREATMENT

The goals of therapy are as follows: Decompression of the joint space and removal of inflammatory debris by adequate drainages sterilization of the joint through the use of appropriate antimicrobial agents; relief of pain; and prevention of joint deformity.

It includes the choice of antibiotics. It is based on the microscopic examination of Gram stained smear. Surgical drainage should be performed especially if hip and shoulder are involved.

#### Antibiotic Therapy

Antimicrobial therapy should be instituted immediately after blood cultures and joint fluid samples are obtained. Empiric, initial antibiotic choice is

based on the likely pathogens at various ages, the results of Gram stain of the joint aspirate, and any special considerations dictated by the patient's underlying medical problems or clinical situation.

Empiric choice of antimicrobials is similar to that recommended for osteomyelitis, and regimens for all age groups should include an antistaphylococcal agent with coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) as dictated by local prevalence.

If *Neisseria gonorrhoeae* is a consideration, ceftriaxone, or cefotaxime should be used. Parenteral antibiotics are used initially and continued until there is no further need for surgical intervention and the child is afebrile with clinical improvement and improvement of laboratory parameters. Exact length of therapy is dependent on the clinical situation, the patient's response, and the particular organism. Traditionally, therapy is continued for at least 2 weeks after the patient is afebrile, joint fluid accumulation has resolved, and laboratory parameters have normalized.

Antibiotics can be selected based on the child's age, results of the Gram stain, and culture of the aspirated pus. Reasonable empiric therapy in infants is nafcillin or oxacillin plus a third generation cephalosporin. An antistaphylococcal agent alone is usually adequate for children over age 5 years. For staphylococcal infections, 3 weeks of therapy is recommended; for other organisms, 2 weeks is usually sufficient.

Oral therapy may be begun when clinical signs have improved markedly. It is not necessary to give intra-articular antibiotics, because good levels are achieved in the synovial fluid.

In neonates, an antistaphylococcal penicillin, such as nafcillin or oxacillin (150–200 mg/kg/day divided q6h IV), and a broad-spectrum cephalosporin, such as cefotaxime (150–225 mg/kg/day divided q8h IV), provide coverage for the *S. aureus*, group B *Streptococcus*, and gram-negative bacilli. If MRSA is a concern, vancomycin is selected instead of nafcillin or oxacillin.

In older infants and children with septic arthritis, empirical therapy to cover for *S. aureus*, streptococci, and *K. kingae* includes cefazolin (100–150 mg/kg/day divided q8h) or nafcillin (150–200 mg/kg/day divided q6h).

In areas where methicillin resistance is noted in 10% of community-acquired methicillin-resistant *S. aureus* (CAMRSA) strains, including an antibiotic that is effective against CAMRSA isolates is suggested. Clindamycin (40 mg/kg divided q8h) and vancomycin (15 mg/kg q6h IV) are alternatives

when treating CAMRSA infections. For immunocompromised patients, combination therapy is usually initiated, such as with vancomycin and ceftazidime or with extended-spectrum penicillins and  $\beta$ -lactamase inhibitors with an aminoglycoside.

When the pathogen is identified, appropriate changes in antibiotics are made, if necessary. If a pathogen is not identified and a patient's condition is improving, therapy is continued with the antibiotic selected initially. If a pathogen is not identified and a patient's condition is not improving, reaspiration or the possibility of a noninfectious condition should be considered.

Duration of antibiotic therapy is individualized depending on the organism isolated and the clinical course. Around 10–14 days is usually adequate for streptococci, *S. pneumoniae*, longer therapy may be needed for *S. aureus* and gram-negative infections. Normalization of ESR and CRP in addition to a normal examination supports discontinuing antibiotic therapy. Oral antibiotics can be used to complete therapy once the patient is afebrile for 48–72 hours and is clearly improving.

Intravenous antibiotics for 14–21 days must be used. Chloramphenicol in the dose of 100 mg/kg/24 h in four divided intravenous doses. Ampicillin in the dose of 200 mg/kg/24 h in six divided doses or cefotaxime in the dose of 150 mg/kg/24 h in four divided doses is recommended. If there is no clinical improvement within 48 hours, then the surgical drainage of the infected joint should be undertaken immediately.

In the hip joint, pyogenic arthritis is most easily treated by surgical drainage because the joint is deep and difficult to aspirate and is also inaccessible to thorough cleaning through needle aspiration.

Arthroscopic irrigation and debridement have been successful in treating pyogenic arthritis of the knee. If fever and clinical symptoms do not subside within 24 hours after the treatment is begun, open surgical drainage is indicated.

## Surgical Therapy

Drainage of the infected joint may require repeated aspiration, arthroscopic lavage, or open drainage with lavage. Repeated aspiration may be appropriate in a setting where no surgeon is readily available to perform arthroscopic or open drainage, but drainage with lavage, either via an arthroscopic or an open procedure, is superior because it allows thorough cleansing and removal of inflammatory debris that cannot be evacuated by aspiration. Arthrotomy may not be necessary for infection

of all joints, but is indicated for patients who fail to respond to repeated joint aspirations and in those with infections of the hip (and perhaps the shoulder). Recently, arthroscopic techniques have become more popular and cause less morbidity, with similar results.

Infection of the hip is generally considered a surgical emergency because of the vulnerability of the blood supply to the head of the femur. For joints other than the hip, daily aspirations of synovial fluid may be required. Generally one or two subsequent aspirations suffice. If fluid continues to accumulate after 4–5 days, arthrotomy or video-assisted arthroscopy is needed. At the time of surgery, the joint is flushed with sterile saline solution.

## PROGNOSIS

The prognosis for the patient with pyogenic arthritis is excellent if the joint is drained early, before damage to the articular cartilage has occurred. If infection is present for more than 24 hours, there is dissolution of the proteoglycans in the articular cartilage, with subsequent arthrosis and fibrosis of the joint. Damage to the growth plate may also occur, especially within the hip joint, where the epiphyseal plate is intracapsular.

Sequelae of septic arthritis include joint deformity and residual dysfunction, abnormal bone growth, and in the hip, avascular necrosis of the femoral head. Risk factors for subsequent complications include delay in drainage, age <1 year, involvement of the hip or shoulder, adjacent osteomyelitis, and infection with *S. aureus*.

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# Tetanus Neonatorum

## PRESENTING COMPLAINTS

A 6-day-old newborn was brought with the complaints of:

- General rigidity of the body since 2 days
- Breathlessness since 2 days
- Not taking feeds since 1 day
- Excessive crying since 1 day

## History of Presenting Complaints

A 6-day-old boy was brought to the hospital with history of excessive crying and not taking feeds since 2 days. His mother had noticed that child was apparently normal till the 3rd day. She noticed that her son was crying excessively. She was trying to feed him and thinking that he might be hungry. But her efforts used to be in vain.

Mother had also noted that child had generalized rigidity and bending of the body in

extension since 2 days. There was also history of fever, moderate to high degree. This was not associated with chills and rigors. There was also history of respiratory distress.

## Past History of the Patient

He was the only sibling of nonconsanguineous marriage. The child was born at home at full term by normal delivery. Delivery was conducted by untrained personnel. The baby cried immediately after the delivery. Mother was doubtful whether she had been received tetanus toxoid antenatally.

## EXAMINATION

On examination, the child was moderately built and nourished. He was crying excessively and was not taking feeds. The mouth of the child was kept slightly opened. There was generalized rigidity. At the time of the examination, the child was cyanosed as a result of the spasm of the larynx and respiratory muscles.

Anthropometric measurements included, the length of the child was 51 cm (50th centile), the weight was 3 kg (50th centile). The head circumference was 34 cm. He was febrile, 38°C. Heart rate was 120 per minute, the respiratory rate was 38 per minute. Blood pressure recorded was 50/30 mm Hg.

There was no pallor, no lymphadenopathy and no edema. Cyanosis was evident. Umbilical stump was infected. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 10,200 cells/cu mm
ESR	: 20 mm in the 1st hour
CRP	: 1900 µg/L
Blood culture and sensitivity	: No growth
X-ray chest	: Normal
CSF examination	: Normal

### CASE AT A GLANCE

#### Basic Findings

Length	: 51 cm (50th centile)
Weight	: 3 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 120 per minute
Respiratory rate	: 38 per minute
Blood pressure	: 50/30 mm Hg

#### Positive Findings

##### History

- Excessive crying
- Not taking feeds
- Muscular rigidity
- Cyanosis
- Home delivery

##### Examination

- Excessive crying
- Not taking feeds
- Cyanosis
- Tachycardia
- Tachypnea
- Infected umbilical stump

##### Investigation

- Normal



## DISCUSSION

Tetanus neonatorum is caused by gram-positive motile, anaerobic spore-bearing bacillus called *Clostridium tetani*. The organism enters the body through the open wounds by the soil containing clostridial spores from animal manure. The toxin reaches the central nervous system (CNS) by retrograde axon transport, is bound to cerebral gangliosides, and is thought to increase reflex excitability in neurons of the spinal cord by blocking function of inhibitory synapses. Intense muscle spasms result. It produces powerful neurotoxin, i.e., tetanospasmin enters into the circulation. It enters into the motor end plates. It spreads to the nervous system along with the axon cylinders of the motor nerves.

## ETIOLOGY

Tetanus is an acute, spastic paralytic illness historically called lockjaw that is caused by the neurotoxin produced by *Clostridium tetani*, a motile, gram-positive, spore-forming obligate anaerobe whose natural habitat worldwide is soil, dust, and the alimentary tracts of various animals. *C. tetani* forms spores terminally, producing a drumstick or tennis racket appearance microscopically. Tetanus spores can survive boiling but not autoclaving, whereas the vegetative cells are killed by antibiotics, heat, and standard disinfectants. Unlike many clostridia, *C. tetani* is not a tissue-invasive organism and instead causes illness through the effects of a single toxin, tetanospasmin, more commonly referred to as tetanus toxin. Tetanospasmin in the second most poisonous substance known, surpassed in potency only by botulinum toxin. The human lethal dose of tetanus toxin is estimated to be  $10^{-5}$  mg/kg.

## PATHOGENESIS

Tetanus occurs after introduced spores germinate, multiply, and produce tetanus toxin in the low oxidation-reduction potential of an infected injury site. A plasmid carries the toxin gene. Toxin is released after vegetative bacterial cell death and lysis.

Tetanus toxin (and the botulinum toxins) is a 150 kDa simple protein consisting of a heavy chain (100 kDa) and a light (50 kDa) chain joined by a single disulfide bond. Tetanus toxin binds at the neuromuscular junction and enters the motor nerve by endocytosis, after which it undergoes retrograde axonal transport to the cytoplasm of the alpha-motoneuron. In the sciatic nerve, the transport rate was found to be 3.4 mm/h.

The toxin exits the motoneuron in the spinal cord and next enters adjacent spinal inhibitory interneurons, where it prevents release of the neurotransmitters glycine and Gamma aminobutyric acid. Tetanus toxin thus blocks the normal inhibition of antagonistic muscles on which voluntary coordinated movement depends; as a consequence, affected muscles sustain maximal contraction and cannot relax. The autonomic nervous system is also rendered unstable in tetanus. Because *C. tetani* is not an invasive organism, its toxin-producing vegetative cells remain where introduced into the wound, which may display local inflammatory changes and a mixed bacterial flora.

The phenomenal potency of tetanus toxin is enzymatic. The light chain of tetanus toxin (and of several botulinum toxins) is a zinc containing endoprotease whose substrate is synaptobrevin, a constituent protein of the docking complex that enables the synaptic vesicle to fuse with the terminal neuronal cell membrane. The heavy chain of the toxin contains its binding and internalization domains.

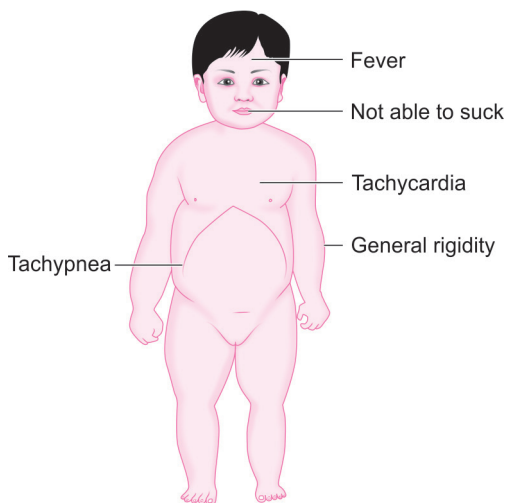
In many cases, no history of a wound can be obtained. In the newborn, usually in underdeveloped countries, infection generally results from contamination of the umbilical cord. The incubation period typically is 4–14 days but may be longer.

Tetanus spores can survive boiling but not autoclaving, whereas vegetative cells are killed by antibiotics, heat and disinfectant. The toxin is produced by vegetative form.

## CLINICAL FEATURES (FIG. 1)

The symptom is often mild pain at the site of inoculation, followed by hypertonicity and spasm of the regional muscles. The most common age at the onset of the symptoms is 3–15 days. Excessive unexplained crying followed by the refusal of the feeds is seen. The mouth is kept slightly opened due to pull and spasm of the neck muscles.

Neonatal tetanus, the first signs are irritability and inability to feed. The infant may then develop stiffness of the jaw and neck, increasing dysphagia, and generalized hyper-reflexia with rigidity and spasms of all muscles of the abdomen and back (opisthotonos). The facial distortion resembles a grimace (risus sardonicus) The sardonic smile, i.e., risus sardonicus, results from intractable spasm of facial and buccal muscles (Fig. 2). Paralysis or diminished movement, stiffness and rigidity to the touch, and spasms with or without opisthotonos,



**Fig. 1:** Clinical features.



**Fig. 2:** Neonatal tetanus.  
(For color version see Plate 4)

are characteristic. The umbilical stump may hold remnants of dirt, dung, clotted blood, or serum, or it may appear relatively benign.

Characteristically, difficulty in opening the mouth (trismus) is evident within 48 hours. Lock jaw or reflex spasm is followed by spasm of limbs, spasm of the larynx and respiratory muscles characteristically induced by stimuli of touch, noise and bright light results in episodes of apnea and cyanosis.

Choking and dysphagia occur due to the spasm of the pharyngeal muscles. There is generalized rigidity and opisthotonus in extension. Difficulty in swallowing and convulsions triggered by minimal

stimuli such as sound, light, or movement may occur. There will be episodes of apnea and cyanosis due to the spasm of the larynx and respiratory muscle. Spasms are characteristically induced by the touch, noise and light. Spasms are less marked in preterm babies. Individual spasms may last for seconds or minutes. Recurrent spasms are seen several times each hour, or they may be almost continuous. Fever, tachycardia and tachypnea are present. Umbilical stump may show the evidence of sepsis.

The convulsions are characterized by sudden, severe tonic contractions of the muscle. There is first clinching, flexion, adduction of arms and hyperextension of the legs. But there are no changes in sensorium.

In most cases, the temperature is normal or only mildly elevated. A high or subnormal temperature is bad prognostic sign. Patients are fully conscious and lucid.

A profound circulatory disturbance associated with sympathetic over activity may occur on the 2nd to 4th day, which may contribute to the mortality rate. This is characterized by elevated blood pressure, increased cardiac output, tachycardia ( $>20$  beats/min), and arrhythmias.

Constipation persists until the spasms are relieved. Intercurrent infections, dehydration and acidosis may complicate the clinical picture.

Cephalic tetanus follows head injury and otitis media. Sometimes it may follow the generalized tetanus. Cranial nerve involvement is present.

#### ESSENTIAL DIAGNOSTIC POINTS

- History of skin wound
- Not immunized child
- *Trismus*: Spasms jaw muscles
- Stiffness of neck, back and abdominal muscles
- Hyperirritability and hyperreflexia
- Generalized, episodic muscle contraction
- No altered sensorium

#### GENERAL FEATURES

- Lock jaw
- *Risus sardonius*
- Convulsions
- No altered sensorium
- Choking
- Opisthotonus

### DIAGNOSIS

The picture of tetanus is one of the most dramatic in medicine, and the diagnosis may be established clinically. The typical setting is an unimmunized

patient (and/or mother) who was injured or born within preceding 2 weeks, who presents with trismus, other rigid muscles, and with clear sensorium.

There may be a mild polymorphonuclear leukocytosis. The cerebrospinal fluid (CSF) is normal with the exception of mild elevation of opening pressure.

Serum muscle enzymes may be elevated. Transient electrocardiographic and electroencephalographic abnormalities may occur. Anaerobic culture and microscopic examination of pus from the wound can be helpful, but *C. tetani* is difficult to grow, and the drumstick-shaped gram-positive bacilli often cannot be found.

#### LABORATORY SALIENT FINDINGS

- Polymorphonuclear leukocytosis
- Serum muscle enzymes may be elevated
- ECG and EEG abnormalities
- Anaerobic culture examination of pus: drumstick gram +ve bacilli

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes retropharyngeal abscess, trauma, meningitis and poliomyelitis. Poliomyelitis is characterized by asymmetric paralysis in an incompletely immunized child. The history of an animal bite, absence of trismus, and CSF pleocytosis suggest rabies. Local infections of the throat and jaw should be easily recognized. Bacterial meningitis, phenothiazine reactions, decerebrate posturing, narcotic withdrawal, spondylitis, and hypocalcemic tetany may be confused with tetanus.

### MANAGEMENT

The aims of treatment are airway maintenance, prevention of further toxin absorption, relieving clinical features, controlling automatic instability and antibiotics.

Airway management may require intubation and mechanical ventilation, especially in severe cases.

Management of tetanus requires eradication of *C. tetani* and the wound environment conducive to its anaerobic multiplication, neutralization of all accessible tetanus toxin, control of seizures and respiration, palliation, provision of meticulous supportive care, and, finally, prevention of recurrences.

Surgical wound excision and debridement are often needed to remove the foreign body or devitalized tissue that created anaerobic growth

conditions. Surgery should be performed promptly after administration of human tetanus immunoglobulin (TIG) and anti-serum. Excision of the umbilical stump in the neonate with tetanus is no longer recommended.

Tetanus toxin cannot be neutralized by TIG after it has begun its axonal ascent to the spinal cord. TIG should be given as soon as possible as to neutralize toxin that diffuses from the wound into the circulation before the toxin can bind at distant muscle groups. The optimal dose of TIG has not been determined. A single intramuscular injection of 500–1000 IU of TIG is sufficient to neutralize systemic tetanus toxin, but total doses as high as 3,000–6,000 IU are also recommended. Infiltration of TIG into the wound is now considered unnecessary. If TIG is unavailable, use of human intravenous immunoglobulin may be necessary. Intravenous immunoglobulin contains 4–90 units/mL of TIG; the optimal dosage of intravenous immunoglobulin for treating tetanus is not known, and its use is not approved for this indication.

Another alternative is equine- or bovine-derived tetanus antitoxin (TAT). The usual dose of TAT is 50,000–100,000 units, with half given intramuscularly and half intravenously, but as little as 10,000 units may be sufficient. Approximately 15% of patients are given the usual dose of TAT experience serum sickness. When TAT is used, it is essential to check for possible sensitivity to horse serum; desensitization may be needed. The human derived immunoglobulins are much preferred because of their longer half-lives (30 days) and the virtual absence of allergic and serum sickness adverse effects. Intrathecal TIG, given to neutralize tetanus toxin in the spinal cord, is not effective.

Penicillin G (100,000 units/kg/day divided every 4–6 hours IV for 10–14 days) remains the antibiotic of choice because of its effective clostridiocidal action and its diffusibility, which is an important consideration because blood flow to injured tissue may be compromised. Metronidazole (500 mg every 8 hours IV for adults) appears to be equally effective. Erythromycin and tetracycline (for persons >8 years of age) are alternatives for penicillin-allergic patients.

All patients with generalized tetanus need muscle relaxants. Diazepam provides both relaxation and seizure control. The initial dose of 0.1–0.2 mg/kg every 3–6 hours given intravenously is subsequently titrated to control the tetanic spasms, after which the effective dose is sustained for 2–6 weeks before a tapered withdrawal. Magnesium sulfate, other benzodiazepines

(midazolam), chlorpromazine, dantrolene, and baclofen are also used. Diazepam prevents by GABA-mediated central inhibition. Intrathecal baclofen produces such complete muscle relaxation that apnea often ensues; like most other agents listed, baclofen should be used only in an intensive care unit setting. Oral drugs used for severe spasms include pancuronium bromide. Autonomic instability is controlled with the use of alpha and beta adrenergic blockers and IV magnesium.

The highest survival rates in generalized tetanus are achieved with neuromuscular blocking agents such as vecuronium and pancuronium, which produce a general flaccid paralysis that is then managed by mechanical ventilation. Autonomic instability is regulated with standard alpha- or beta (or both) blocking agents; morphine has also proved useful.

## SUPPORTIVE CARE

Meticulous supportive care in a quiet, dark, secluded setting is most desirable. Because tetanic spasms may be triggered by minor stimuli, the patient should be sedated and protected from all unnecessary sounds, sights, and touch. All therapeutic and other manipulations must be carefully scheduled and coordinated.

Cardiorespiratory monitoring, frequent suctioning, and maintenance of the patient's substantial fluid, electrolyte, and caloric needs are fundamental. Careful nursing attention to mouth, skin, bladder, and bowel function is needed to avoid ulceration, infection, and obstipation. Prophylactic subcutaneous heparin may be of value but must be balanced with the risk for hemorrhage.

Endotracheal intubation may not be required, but it should be done to prevent aspiration of secretions before laryngospasm develops. A tracheostomy kit should be immediately at hand for unintubated patients. Endotracheal intubation and suctioning easily provoke reflex tetanic seizures and spasms, so early tracheostomy should be considered in severe cases not managed by pharmacologically induced flaccid paralysis. Therapeutic botulinum toxin has been used for this purpose, that is, to overcome trismus.

## COMPLICATIONS

The seizures and the severe, sustained rigid paralysis of tetanus predispose the patient to many complications. Aspiration of secretions and pneumonia may have begun before the first medical

attention was received. Maintaining airway patency often mandates endotracheal intubation and mechanical ventilation with their attendant hazards, including pneumothorax and mediastinal emphysema.

The seizures may result in lacerations of the mouth or tongue, in intramuscular hematomas or rhabdomyolysis with myoglobinuria and renal failure, or in long bone or spinal fractures. Venous thrombosis, pulmonary embolism, gastric ulceration with or without hemorrhage, paralytic ileus, and decubitus ulceration are constant hazards. Excessive use of muscle relaxants, which are an integral part of care, may produce iatrogenic apnea. Cardiac arrhythmias, including asystole, unstable blood pressure, and labile temperature regulation reflect disordered autonomic nervous system control that may be aggravated by inattention to maintenance of intravascular volume needs.

## PROGNOSIS

The most important factor that influences outcome is the quality of supportive care. Mortality is highest in the very young and the very old. A favorable prognosis is associated with a long incubation period, absence of fever, and localized disease.

An unfavorable prognosis is associated with onset of trismus <7 days after injury and with onset of generalized tetanic spasms <3 days after onset of trismus. Sequelae of hypoxic brain injury, especially in infants, include cerebral palsy, diminished mental abilities, and behavioral difficulties. Most fatalities occur within the 1st week of illness. Reported case fatality rates for generalized tetanus are 5–35%, and for neonatal tetanus they extend from <10% with intensive care treatment to >75% without it. Cephalic tetanus has an especially poor prognosis because of breathing and feeding difficulties.

Prognosis is worse if onset of symptoms occur within the 1st week of life, if the interval between lock jaw and the onset of the spasm is less than 48 hours, if high fever and tachycardia are present. Laryngeal spasm resulting in apnea are frequent. Many deaths are due to pneumonia or respiratory failure. If the patient survives 1 week, recovery is likely.

## PREVENTION

Tetanus is an entirely preventable disease. A serum antibody titer of >0.01 units/mL is considered protective.

Active immunization should begin in early infancy with combined diphtheria toxoid-tetanus toxoid-acellular pertussis (DTaP) vaccine at 2, 4, 6 and 15–18 months of age, with boosters at 4–6 years (DTaP) and 11–12 years (Tdap) of age and at 10 years intervals thereafter throughout adult life with tetanus and reduced diphtheria toxoid (Td).

Immunization of women with tetanus toxoid prevents neonatal tetanus, and pregnant women should receive 1 dose of reduced diphtheria and pertussis toxoids (Tdap) during each pregnancy, preferably at 27–36 weeks gestation.

Arthus reactions (type III hypersensitivity reactions), a localized vasculitis associated with deposition of immune complexes and activation

of complement, are reported rarely after tetanus vaccination. Mass immunization campaigns in developing countries have occasionally provoked a widespread hysterical reaction,

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## PRESENTING COMPLAINTS

A 10-year-old boy was brought with the complaints of:

- Fever since 10 days
- Headache since 10 days
- Tiredness since 5 days
- Loose motion since 3 days

## History of Presenting Complaints

A 10-year-old boy was brought to the hospital with history of fever, lethargy and headache for 10 days. Fever was of moderate-to-high degree, intermittent more in the evening and night. It was associated with chills and rigors. Headache was diffuse in nature and was severe, throbbing type. It used to be relieved by taking analgesics. There was no history of vomiting.

One week back, he had been to an endemic area where malaria was more common. Mother told that for that he had been treated with intravenous (IV)

antibiotics, temperature was present with spikes. Later he developed loose motion.

## Past History of the Patient

He was the eldest sibling of nonconsanguineous marriage. He was born at full term by normal delivery. There were no significant postnatal events. His developmental milestones were normal. He had been completely immunized. His performance at school was good.

## EXAMINATION

The boy was moderately built and nourished. He was looking sick and moderately dehydrated. The anthropometric measurements included, the height was 135 (50th centile) and the weight was 29 kg (75th centile). He was febrile, i.e., 39°C. The pulse rate was 116 per minute and the respiratory rate was 22 per minute. The blood pressure recorded was 100/70 mm Hg. There was pallor, no icterus, and no edema. There was cervical lymphadenopathy.

Per abdomen examination revealed the enlargement of the spleen. Splenomegaly was present about 2 cm below the costal margin. It was nontender. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 8 g/dL
TLC	: 5,200 cells/cu mm
DLC	: $P_{65} L_{30} M_2 E_1$
Platelet count	: 650,000 cells/cu mm
Blood culture and sensitivity	: No growth
Widal test	: O 1:320 H 1:320

## DISCUSSION

Fever, headache, associated splenomegaly, and loose motion lead to the provisional diagnosis of

### CASE AT A GLANCE

#### Basic Findings

Height	: 135 cm (50th centile)
Weight	: 29 kg (75th centile)
Temperature	: 39°C
Pulse rate	: 116 per minute
Respiratory rate	: 22 per minute
Blood pressure	: 100/70 mm Hg

#### Positive Findings

##### History

- Fever with rigors
- Headache
- IV antibiotics did not control temperature
- Loose motions

##### Examination

- Febrile
- Cervical lymphadenopathy
- Splenomegaly

##### Investigation

- Hb: Anemia
- TLC: Leukopenia
- Widal test: Positive

enteric fever and malaria. The diagnosis of typhoid is favored because of the presence of leukopenia especially neutropenia. Diagnosis of typhoid is mainly made by blood culture and sensitivity in the 1st week.

## ETIOLOGY

Typhoid fever is caused by *Salmonella enterica* serovar *typhi* (*S. typhi*), a gram-negative bacterium. A very similar but often less severe disease is caused by *Salmonella paratyphi A* and rarely by *Salmonella paratyphi B* and *Salmonella paratyphi C*.

## PATHOGENESIS

Typhoid fever is caused by the gram-negative bacillus *Salmonella typhi*. Paratyroid fevers, which are usually milder but may be clinically indistinguishable are caused by *Salmonella paratyphi A*, *Salmonella schottmulleri* or *Salmonella hirschfeldii* (formerly *Salmonella paratyphi A*, *B* and *C*), children have a shorter incubation period than do adults (usually 5–8 days instead of 8–14 days).

Enteric fever occurs through the ingestion of the organism, and a variety of sources of fecal contamination have been reported, including street foods and contamination of water reservoirs, with an incubation period ranging from 4 to 14 days and depending on the inoculating dose of viable bacteria.

Typhoid fever is transmitted by the feco-oral route and by contamination of food and water. Unlike other *Salmonella* species, there are no animal reservoirs of *S. typhi*; each case is the result of direct or indirect contact with the organism or with an individual who is actively infected or a chronic carrier.

The infected persons excrete the bacilli in stools and urine. Food and water may be contaminated by hands of carrier of patients. It is transmitted by ingestion of the infected food, milk, or water. The period of infectivity or communicability lasts as long as bacteria are present in excreta.

After ingestion, *S. typhi* organisms are thought to invade the body through the gut mucosa in the terminal ileum, possibly through specialized antigen-sampling cells known as M cells that overlie gut-associated lymphoid tissues, through enterocytes, or via a paracellular route. *S. typhi* crosses the intestinal mucosal barrier after attachment to microvilli by an intricate mechanism

involving membrane ruffling actin rearrangement, and internalization in an intracellular vacuole.

*S. typhi* has three main antigens O, H and Vi, and a number of phage types. It survives intracellularly in the tissue of various organs. The factors which influence the onset of typhoid fever in man are the infecting dose and virulence of organism.

*S. typhi* expresses virulence factors that allow it to downregulate the pathogen recognition receptor-mediated host inflammatory response. Within the Peyer's patches in the terminal ileum, *S. typhi* can traverse the intestinal barrier through several mechanisms, including the M cells in the follicle-associated epithelium, epithelial cells, and dendritic cells. At the villi, *Salmonella* can enter through the M cells or by passage through or between compromised epithelial cells.

After passing through the intestinal mucosa, *S. typhi* organisms enter the mesenteric lymphoid system and then pass into the blood-stream via the lymphatics. This primary bacteremia is usually asymptomatic, and blood culture results are frequently negative at this stage of the disease. The bloodborne bacteria are disseminated throughout the body and are thought to colonize the organs of the reticuloendothelial system, where they may replicate within macrophages. After a period of bacterial replication, *S. typhi* organisms are shed back into the blood, causing a secondary bacteremia that coincides with the onset of clinical symptoms and marks the end of the incubation period.

The organism enters the body through the walls of the intestinal tract and following a transient bacteremia, multiplies in the reticuloendothelial cells of the liver and spleen. Persistent bacteremia and symptoms then follow. The organism does not invade the mucosa. But it goes into the submucosal tissue where they proliferate in the lymphoid tissue of the ileum. Peyer's patches are swollen and show marked round cell infiltration. Macrophages engulf the bacteria and they carry them to distant site.

The mesenteric lymph nodes, liver and spleen are hyperemic and generally reveal the area of focal necrosis. Reinfection of the intestine occurs as organisms are excreted in the bile. Bacterial emboli produce the characteristic skin lesions (rose spots). Hyperplasia of the reticuloendothelial system with proliferation of mononuclear cell is predominant finding. Symptoms in children may be mild or severe, but children under age 5 years rarely have severe typhoid fever.

## CLINICAL FEATURES (FIG. 1)

The primary sources of infection are feces and urine of the carrier cases. The secondary sources are contaminated finger and food.

The incubation period of typhoid fever is usually 7–14 days but depends on the infecting dose and ranges between 3 and 30 days. Many factors influence the severity and overall clinical outcome of the infection. They include the duration of illness before the initiation of appropriate therapy, choice of antimicrobial treatment, age, previous exposure or vaccination history, virulence of the bacterial strain, quantity of inoculum ingested, and several host factors affecting immune status.

In children, the onset of typhoid fever is sudden rather than insidious, with malaise, headache, crampy abdominal pains and distension, and sometimes constipation followed within 48 hours by diarrhea, high fever and toxemia.

The presentation of typhoid fever may also differ according to age. Diarrhea, toxicity, and complications such as disseminated intravascular coagulopathy are also more common in infancy, resulting in higher case fatality rates. However, some of the other features and complications of typhoid fever seen in adults, such as relative bradycardia, neurologic manifestations, and gastrointestinal bleeding, are rare in children.

Typhoid fever usually manifests as high-grade fever with a wide variety of associated features, such as generalized myalgia, abdominal pain, hepatosplenomegaly, abdominal pain, and anorexia. In children, diarrhea may occur in the earlier stages of the illness and may be followed by constipation. In about 25% of cases, a macular

or maculopapular rash (rose spots) may be visible around the 7th–10th day of the illness, and lesions may appear in crops of 10–15 on the lower chest and abdomen and last 2–3 days. These lesions may be difficult to see in dark-skinned children.

An encephalopathy may be seen with irritability, confusion, delirium and stupor. Vomiting and meningismus may be prominent in infants and young children. The classic lengthy three stage disease seen in adult patients is often shortened in children. The prodrome may last only 2–4 days, the toxic stage only 2–3 days and the defervescence stage 1–2 weeks.

During the prodromal stage, physical findings may be absent or there may merely be some abdominal distension and tenderness, meningismus, mild hepatomegaly and minimal splenomegaly.

The typical typhoidal rash (rose spots) is present in 10–15% of children. It appears during the second week of the disease and may erupt in crops for the succeeding 10–14 days. Rose spots are erythematous maculopapular lesions 2–3 mm in diameter that fade on pressure. They are found principally on the trunk and chest and generally, disappear within 3–4 days. The lesions usually number fewer than 20.

If no complications occur, the symptoms and physical findings gradually resolve within 2–4 weeks; however, the illness may be associated with malnutrition in a number of affected children. Although enteric fever caused by *S. paratyphi* organisms has been classically regarded as milder illness, there have been several outbreaks of infection with drug-resistant *S. paratyphi* A, suggesting that paratyphoid fever may also be severe, with significant morbidity and complications.

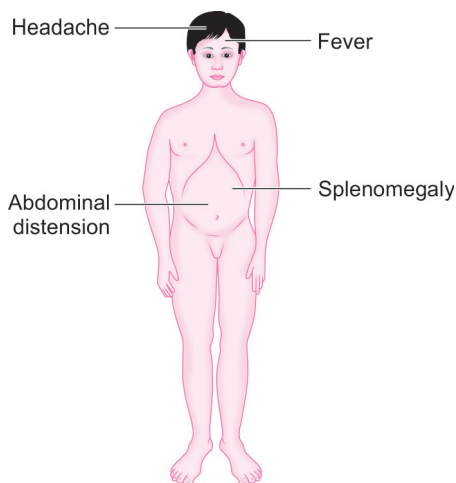


Fig. 1: Clinical features.

### ESSENTIAL DIAGNOSTIC POINTS

- Insidious or acute-onset headache, vomiting, anorexia, constipation, diarrhea, ileus, and high fever
- Meningismus, splenomegaly
- Leukopenia
- Positive stool, blood, bone marrow, and urine culture

In severe toxic state, there is altered sensorium. Child may be in apathy and stuporous. Child may be muttering in delirium. This peculiar state is called typhoid state.

Convalescent carriers excrete *Salmonella* for 3 months after the illness. Few of them may become permanent carrier. Permanent carriers excrete *Salmonella* in their stool for more than a

year after an episode of enteric fever. This occurs in 1–4% of cases. Carrier state is more common under 5 years of age. Few may continue to excrete the organism in urine.

Permanent carrier continues to excrete *Salmonella* their stool for more than 1 year after an episode of enteric fever. It is more common among less than 5 years of age.

#### GENERAL FEATURES

- Fever
- Chills and rigors
- Loose motion
- Rashes

## DIAGNOSIS

### Complete Blood Count

Change in complete blood count (CBC) is non-specific. Leukopenia is found in 20–25% cases whereas leukocytosis makes the diagnosis less probable. White blood cell (WBC) count remains low mostly. In differential count, absolute eosinopenia and thrombocytopenia may be seen. Presence of severe anemia is unlikely, if present, points toward complications such as perforation, hemolysis or an alternative diagnosis such as malaria.

### Biochemical

Mild elevation of bilirubin and serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) may occur.

### Culture

Definitive diagnosis is by isolation of organism by culture of different specimen.

#### Blood Culture

It is gold standard investigation with overall sensitivity of 50% and specificity of 100%. Sensitivity is maximum in first week and reduces with time.

BACTEC, automated blood culture system certainly increases isolation rate. Blood culture should be clone in all suspected cases as positive culture riot only unequivocally establishes the diagnosis but also gives the sensitivity pattern which is important in this era of multidrug-resistant typhoid fever (MDRTF).

#### Stool, Urine, and Other Culture

These are not done routinely. Bacilli can be isolated in third week if untreated. Stool specimen

of adequate amount should be processed within 2 hours or should be kept in 4°C. For the detection of carrier, several samples should be examined because of irregular shedding of organism. Sensitivity of urine culture is very poor. Duodenal string and skin snip culture of rose spots is of academic interest only.

## Serological Tests

No tests are enough sensitive or specific to replace culture-based diagnosis.

### Widal Test

It detects agglutinating antibodies against the somatic O and flagellar H antigen of *S. typhi*, *S. paratyphi A* and *B*. “O” antigen is also shared by other *Salmonella* species and other members of Enterobacteriaceae family. Anti-O titer is mainly immunoglobulin M (IgM) type, rises and falls sharply early in the illness whereas anti-H titer is both IgM and immunoglobulin G (IgG) type rises late in the illness and persists for longer time.

Conventionally, positive Widal implies rising titer in paired samples done at a gap of weeks but use of antibiotics dampens the immune response and may prevent rise in titer. In endemic area, baseline antibodies are present due to repeated subclinical infections with *Salmonella* and other Enterobacteriaceae. This antibody titer varies with age, socioeconomic condition, urban or rural area and prior immunization status. For optimal result, Widal test should be done by tube method after 5–7 days of fever and single result of 1:160 against both O and H antigen should be taken as cutoff value for diagnosis.

It is most widely used diagnostic tool but the sensitivity and specificity is suboptimal. It may be negative in up to 30% culture-positive enteric fever.

### Enzyme Immunoassay Test or Typhidot Test

This is a simple, rapid test for early diagnosis and has high positive and negative predictive values. It detects IgM and IgG antibodies against outer membrane protein of typhi and is commercially available as typhidot. Detection of IgM indicates acute infection in early stage. Whereas IgG antibodies can persist till 2 years following an infection. So, the test cannot distinguish between acute infection and convalescence phase.

This test has been improved in modified typhidot M test which detects only IgM antibodies.

### TUBEX Test

Positive test detect only IgM antibodies against O9-antigens, specifically found in group D *Salmonella*. It is not positive with other groups of *Salmonella* like paratyphoid.

### Antigen Detection Test

To detect serum or urinary O, H or Vi antigens have suboptimal with variable sensitivity and specificity.

#### LABORATORY SALIENT FINDINGS

- Positive blood culture in the 1st week
- Positive stool culture after 1st week
- Leukopenia
- *Serological tests*: Widal test, typhidot test
- Proteinuria
- Thrombocytopenia
- Mild elevation of liver enzymes

### COMPLICATIONS

Complications occur in about 30% of unattended patients. These include bronchitis, pneumonia, myocarditis, liver abscess, diarrhea and encephalitis, perforation of the intestine, peritonitis and chronic osteomyelitis.

The most serious complications of typhoid fever are gastrointestinal hemorrhage (2–10%) and perforation (1–3%). They occur toward the end of the second week or during the third week of the disease.

Intestinal perforation is one of the principal causes of death. The site of perforation generally is the terminal ileum or cecum. The clinical manifestations are indistinguishable from those of acute appendicitis, with pain, tenderness and rigidity in the right lower quadrant. The X-ray finding of the free air in the peritoneal cavity is diagnostic.

Bacterial pneumonia, meningitis, septic arthritis, abscesses and osteomyelitis are uncommon complications, particularly if specific treatment is given promptly. Shock and electrolyte disturbances may lead to death.

About 1–3% of patients become chronic carriers of *S. typhi*. Chronic carriage is defined as excretion of typhoid bacilli for more than a year; but carriage is often lifelong. Adults with underlying biliary or urinary tract disease are much more likely than children to become chronic carriers.

Relapse may occur up to 2 weeks after the termination of therapy. Complications occur in about 30% of untreated patients.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes malaria, kala-azar, brucellosis, infectious mononucleosis and leptospirosis.

### TREATMENT

An early diagnosis of typhoid fever and institution of appropriate treatment are essential. The vast majority of children with typhoid fever can be managed at home with oral antibiotics and close medical follow-up for complications or failure of response to therapy. Patients with persistent vomiting, severe diarrhea, and abdominal distention may require hospitalization and parenteral antibiotic therapy.

There are general principles of typhoid fever management. Adequate rest, hydration, and attention are important to correct fluid and electrolyte imbalance. Antipyretic therapy (acetaminophen 10–15 mg/kg every 4–6 hours PO) should be provided as required. A soft, easily digestible diet should be continued unless the patient has abdominal distention or ileus.

Antibiotic therapy is critical to minimize complications. It has been suggested that traditional therapy with either chloramphenicol or amoxicillin is associated with relapse rates of 5–15% and 4–8%, respectively, whereas use of the quinolones and third-generation cephalosporins is associated with higher cure rates.

The antibiotic treatment of typhoid fever in children is also influenced by the prevalence of antimicrobial resistance. Over the past two decades, emergence of multidrug-resistant strains of *S. typhi* (i.e., isolates fully resistant to amoxicillin, trimethoprim-sulfamethoxazole, and chloramphenicol) has necessitated treatment with fluoroquinolones, which are the antimicrobial drug of choice for treatment of salmonellosis in adults, with cephalosporins as an alternative. The emergence of resistance to quinolones places tremendous pressure on public health systems because alternative therapeutic options are limited.

In addition to antibiotics, the importance of supportive treatment and maintenance of appropriate fluid and electrolyte balance must be underscored. Although additional treatment with dexamethasone (3 mg/kg for the initial dose, followed by 1 mg/kg every 6 hours for 48 hours is recommended for severely ill patients with shock, obtundation stupor, or coma; corticosteroids should be administered only under strict controlled



conditions and supervision, because they may mask signs of abdominal complications.

Antimicrobial susceptibility testing and local experience are used to guide therapy. Equally effective regimens for susceptible strains include the following: Oral cefixime at the dose of 20 mg/kg/day (ceiling dose of 1,200 mg) is the drug of choice. Azithromycin 10–20 mg/kg/day is a good second choice.

Trimethoprim sulfamethoxazole (10 mg/kg trimethoprim and 50 mg/kg sulfamethoxazole per day orally in two or three divided doses), amoxicillin (100 mg/kg/day in four divided doses) and ampicillin (100–200 mg/kg/day IV in four divided doses) can be used.

Treatment of carrier is ampicillin 200 mg/kg/day orally. Other drugs used are ceftriaxone and ciprofloxacin.

Third-generation cephalosporins are used for resistant strains. Ceftriaxone and cefotaxime may be used parenterally. Cefixime is efficacious orally. Ciprofloxacin or other fluoroquinolones are efficacious but not approved in children, but may be used for multiple-resistant strains.

Occasionally, the presence of multiple-resistant strains requires the use of chloramphenicol (50–100 mg/kg/day orally or IV in four doses). Treatment duration is 14–21 days. Patients remain febrile for 3–5 days even with appropriate therapy.

For severe illness and complications, IV ceftriaxone and cefotaxime are used in the doses of 100 mg/kg/day and 200 mg/kg/day, respectively. Parenteral treatment is continued until defervescence has occurred, oral intake has improved and complications resolved. Therapy may be switched to oral cefixime to total duration of 14 days of treatment. Other oral drugs can be used are azithromycin, cotrimoxazole, and amoxicillin.

## Treatment of Relapse

Relapses may be treated with the same drug as used for primary therapy; azithromycin is the preferred drug since it is associated with very low relapse rate.

## PREVENTION

Three types of vaccines are available as follows:

1. Heat-killed phenol-preserved whole-cell *S. typhi* vaccine

2. Purified and adjuvanted Vi polysaccharide vaccine

3. Oral live-attenuated Ty21a typhoid vaccine

Globally, two vaccines are currently able for potential use in children. An oral, live-attenuated preparation of the Ty21a strain of *S. typhi* has good efficacy (67–82%) for up to 5 years. Significant adverse effects are rare. The Vi capsular polysaccharide can be used in people 2 years of age and older. It is given as a single intramuscular dose, with a booster every 2 years, and has a protective efficacy of 70–80%. The vaccines are currently recommended, for anyone traveling into endemic areas, but a few countries have introduced large-scale vaccination strategies. Several large-scale demonstration projects using the Vi polysaccharide vaccine have demonstrated protective efficacy against typhoid fever across all age groups. Recent Vi-conjugate vaccine has a protective efficacy exceeding in younger children and may offer protection of preschool children and are at risk for the case of enteric or typhoid fever.

## PROGNOSIS

A prolonged convalescent carrier stage may occur in children. Three negative cultures after all antibiotics have been stopped are required before contact precautions are stopped. With early antibiotic therapy, the prognosis is excellent. With early treatment, the mortality rate is less than 1%. Relapse occurs 1–3 weeks later in 10–20% of patients despite appropriate antibiotic treatment.

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## PRESENTING COMPLAINTS

A 6-year-old boy was brought with the complaints of:

- Fever since 2 days
- Headache since 2 days
- Anorexia since 1 day
- Skin lesion since 1 day

## History of Presenting Complaints

A 6-year-old boy was brought to the pediatric outpatient department with history of skin lesions all over the body. Mother complained that his son was absolutely normal previous day. It started suddenly and spread all over the body within 24 hours. Skin lesions included vesicles containing clear water, while lesions were opened. These lesions first appeared on scalp and on face and later over chest and back. His mother had noticed that her son was having a mild degree of fever before development of skin rashes. The symptoms of headache and anorexia were recollected and considered as significant. There was history of itching.

### CASE AT A GLANCE

#### Basic Findings

Height	: 118 cm (75th centile)
Weight	: 19 kg (50th centile)
Temperature	: 39°C
Pulse rate	: 120 per minute
Respiratory rate	: 24 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Fever
- Skin lesions
- Similar attack in school

##### Examination

- Febrile
- Pleomorphic skin lesions

##### Investigation

- Normal

## Past History of the Patient

He was the only child of consanguineous marriage. He was born at full term by normal vaginal delivery. There was no significant postnatal event. Child was breastfed for 3 months and weaning of the food was started at 3rd month according to advice of family doctor. His developmental milestones were normal. He had been completely immunized. His performance at school was good. There was history of similar type of skin lesions at school.

## EXAMINATION

The boy was moderately built and moderately nourished. The signs of moderate dehydration were present. He was lying on the examination table with anxious look. Anthropometric measurements included, the height was 118 cm (75th centile) and the weight was 19 kg (50th centile).

He was febrile, i.e., 39°C. The heart rate was 120 per minute and the respiratory rate was 24 per minute. Blood pressure recorded was 70/50 mm Hg. There was no icterus, no cyanosis, no lymphadenopathy, and no pallor. There were skin rashes of varying morphology. These included vesicle, pustule, and crusted lesions. Itching marks were present. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 8,600 cells/cu mm
DLC	: P <sub>72</sub> L <sub>18</sub> E <sub>5</sub> M <sub>2</sub> B <sub>3</sub>
ESR	: 24 mm in 1st hour
AEC	: 440 cells/cu mm
Chest X-ray	: Normal

## DISCUSSION

It is a highly contagious disease presenting with sudden onset of mild fever, mild constitutional symptoms. The rash is centripetal, pleomorphic appearing (**Fig. 1**) on the first day and has relative short course of illness.



**Fig. 1:** Pleomorphic rash.  
(For color version see Plate 5)

Varicella virus produces primary, latent, and recurrent infections. The primary infection is manifested as chickenpox. It results in establishment of lifelong latent infection of sensory ganglion neurons. Gestational chickenpox can be severe in mother and can cause distinct intrauterine syndrome.

Man is the only reservoir. Children of all ages including the neonates are susceptible with the peak incidence between 5 and 9 years.

Varicella virus is a neurotropic human herpes virus. The patients with varicella are contagious from 24 to 48 hours before appearance of rash till the vesicles are crusted, i.e., usually 3–7 days of the onset of rash. Scab formation occurs and fall by 5–20 days.

Varicella is transmitted by contact with oropharyngeal secretions and the fluid of skin lesions of infected individuals, either by airborne spread or through direct contact. Primary infection (varicella) results from inoculation of the virus onto the mucosa of the upper respiratory tract and tonsillar lymphoid tissue. During the early part of the 10–21 days' incubation period, virus replicates in the local lymphoid tissue and then a brief subclinical viremia spreads the virus to the reticuloendothelial system. Widespread cutaneous lesions occur during a second viremic phase that lasts 3–7 days. Peripheral blood mononuclear cells carry infectious virus, generating new crops of vesicles during this period of viremia.

Varicella is also transported back to the mucosa of the upper respiratory tract and oropharynx during the late incubation period, permitting

spread to susceptible contacts 1–2 days before the appearance of rash. Host immune responses limit viral replication and facilitate recovery from infection.

Widespread cutaneous lesions occur during viremic phase. Mononuclear cells carry the infection. This results in generation of new crops of vesicles for 3–7 days. The lesions begin as macules and quickly develop into papules and vesicles with scab and crust formation. The skin lesions are concentrating on trunk, back and shoulder.

Later the viruses are transported back to respiratory mucosal sites during late incubation period. In immunocompromised state, it results in continued viral replication. This may cause injury to lungs, liver, and brain.

Ballooning degeneration of cells in viscera results in giant cells (Cowdry type A) eosinophilic intranuclear acidophilic inclusion bodies. Foci of necrosis may be present in esophagus, pancreas, liver, genitourinary tract, adrenal, etc. In post-varicella encephalitis, perivascular demyelination may be seen in white matter in brain.

It establishes latent infection of sensory ganglia cells in all individuals who have primary infection. Subsequent reactivation of the latent virus results in herpes zoster. There is vesicular rash in dermatomal distribution. It elicits humeral and cell-mediated immunity.

## CLINICAL FEATURES (FIG. 2)

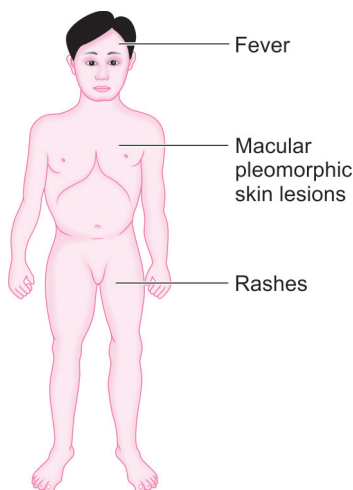
The illness usually begins 14–16 days after exposure. The incubation period can range from 10 to 21 days. Prodromal symptoms include fever, malaise, anorexia, headache, and mild abdominal pain. These symptoms may occur between 24 and 48 hours before the appearance of rash. They may persist 2 and 4 days after onset of rash.

### ESSENTIAL DIAGNOSTIC POINTS

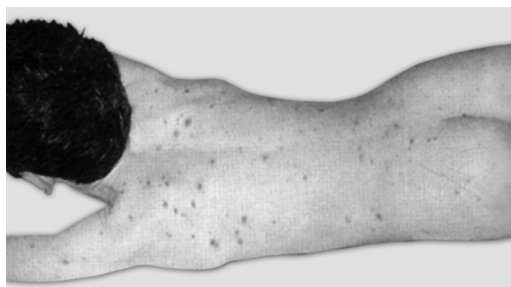
- Contact with varicella or herpes zoster
- Widely spread red macules and papules
- Concentrated on the face and trunk
- Vesicles, pustules, and then crusting in 5–6 days
- Variable fever nonspecific symptoms

The rashes appear on 1st day. The macules quickly developed into papules and vesicles on an erythematous base or areola. New lesions appear for 1–7 days (**Figs. 3 and 4**).

It has a characteristic centripetal distribution. The lesions appear first on the scalp, face or trunk. The lesions being mainly concentrated on trunk, back and shoulders with fewer lesions on face, scalp, extremities, nose, mouth, conjunctiva and vagina.



**Fig. 2:** Clinical features.



**Fig. 3:** Rashes.  
(For color version see Plate 5)



**Fig. 4:** Herpes simplex.  
(For color version see Plate 5)

The initial exanthem consists of pruritic erythematous macules. These later form clear fluid-filled vesicles. Clouding and umbilication begin in 24–48 hours. The initial lesions are crusted. Ulcerative lesions involve oropharynx and vagina.

Vesicular lesions are found in eyelids and conjunctiva.

The usual case consists of mild systemic symptoms followed by crops of red macules that rapidly become small vesicles with surrounding erythema (described as a dew drop on a rose petal), form pustules, become crusted and then scab over and leave no scar. The magnitude of systemic symptoms usually parallels skin involvement. Up to five crops of lesions may be seen. New crops usually stop forming after 5–7 days. Pruritis is often intense. If varicella occurs in the first few months of life, it is often mild as a result of persisting maternal antibody. Once crusting begins, the patient is no longer contagious. Hypopigmentation and hyperpigmentation persists for days to weeks. Scarring is unusual unless secondarily infected.

Severity of the disease is indicated by high temperature 40°C, hemorrhagic rash in child on immunosuppressive drugs such as cortisone. Fetal infection produces embryopathy with limb atrophy, skin scarring, neurological and eye manifestation. Zoster or shingles activate the latent primary infection.

#### GENERAL FEATURES

- Mild fever
- Dehydration
- Decreased appetite
- Centripetal distribution
- Papules, vesicles and erythematous rashes

#### DIAGNOSIS

Diagnosis is clinical and not usually difficult in a typical case. Often a history of exposure to the disease is helpful in reaching the diagnosis. Chickenpox should be differentiated from other exanthemata such as herpes simplex, enteroviral infections, insect bites, and drug reactions.

Leukopenia is typical during the first 72 hours. This is followed by relative or absolute lymphocytosis. Liver function tests are usually mildly elevated.

Cerebrospinal fluid (CSF) examination shows mild lymphocytic pleocytosis and moderate increase in protein.

#### LABORATORY SALIENT FINDINGS

- Leukopenia
- Mildly elevated LFT
- CSF analysis: Mild lymphocytic pleocytosis, moderate increase in protein
- Isolation of virus from vesicles
- ELISA and complement fixation

Varicella pneumonia classically produces numerous bilateral nodular densities and hyperinflation. This is very rare in immunocompetent children. Abnormal chest X-rays are seen more frequently in adults.

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes vesicular rashes by herpes simplex, enterovirus, *Staphylococcus* and drug reactions.

## COMPLICATIONS

The rate of severe or complicated varicella is low among immunocompetent children, but such cases are numerically common in unvaccinated populations. The most frequent complication in the young is secondary bacterial infection of the skin. The other complications of varicella reflect overwhelming viral infection and are more likely to occur in the context of defective cell-mediated immunity.

### Secondary Bacterial Infections

Scratching of the intensely itchy skin lesions of varicella often leads to the introduction of bacteria, typically *Staphylococcus aureus* or *Streptococcus pyogenes*. Local skin infection in a well-child can be treated with an oral antibiotic, with close clinical follow-up. Progression of erythema around lesions, formation of bullae, or development of regional lymphadenitis should prompt consideration of intravenous (IV) antibiotic therapy. Recent varicella confers a significantly increased risk of invasive bacterial disease, particularly group A streptococcal (GAS) infections; these include necrotizing fasciitis, bacteremia, pneumonia, empyema, and toxic shock syndrome. It has been estimated that varicella directly precedes approximately 15% of invasive GAS infections.

### Varicella Pneumonia

Although rates are lower among immunocompetent children, pneumonia commonly accompanies varicella in immunocompromised hosts. Respiratory symptoms (e.g., dyspnea, tachypnea, chest tightness, cough) develop in the context of acute varicella, usually 1–6 days after the onset of the rash, and may progress rapidly to respiratory failure. The severity of clinical signs is a poor guide to prognosis; therefore, the patient with new respiratory symptoms in the context of varicella should be urgently evaluated. IV antiviral therapy and improved intensive care have markedly

improved survival of these patients over recent years, but deaths continue to occur.

Varicella may be life-threatening in immunosuppressed patients (especially those with leukemia or lymphoma or those receiving high doses of steroids). Their disease is complicated by severe pneumonitis, hepatitis, and encephalitis.

Hemorrhagic varicella lesions may be seen without other complications. This is most often caused by autoimmune thrombocytopenia, but hemorrhagic lesions can occasionally represent idiopathic disseminated intravascular coagulation (purpura fulminans).

Neonates born to mothers who develop varicella from 5 days before to 2 days after delivery are at high risk for severe or fatal (5%) disease and must be given varicella-zoster immune globulin and followed closely.

Varicella occurring during the first 20 weeks of pregnancy may cause (2% incidence) congenital infection associated with cicatricial skin lesions, associated limb abnormalities and cortical atrophy.

The complications of varicella-zoster virus (VZV) infection occur with varicella or with reactivation of infection, more commonly in immunocompromised patients. Mild thrombocytopenia occurs in 1–2% of children with varicella and may be associated with transient petechiae. Purpura, hemorrhagic vesicles, hematuria and gastrointestinal bleeding are rare complications that may have serious consequences.

### Neurologic Complications

Varicella is classically associated with three neurologic pictures: (1) cerebellar ataxia, (2) encephalitis, and (3) Reye syndrome. Rarely, it has been associated with Guillain-Barré syndrome, stroke, transverse myelitis, and aseptic meningitis. Cerebellar ataxia complicates approximately 1 in 4,000 cases of varicella and usually follows the onset of rash, making the diagnosis clear. Vomiting and headache often accompany the ataxia, whereas only one-fourth of patients experience neck stiffness or nystagmus. It is not known whether this syndrome results from VZV replication within the central nervous system (CNS) or instead reflects a parainfectious autoimmune process, but the typical timing of onset in the 2nd week following the onset of illness suggests the latter.

Encephalitis occurs in less than 0.1% of cases, usually in the 1st week of illness. It is usually limited to cerebellitis with ataxia, which resolves completely. Diffuse encephalitis can be severe.



Protracted vomiting or a change in sensorium suggests Reye syndrome or encephalitis. Because Reye syndrome usually occurs in patients who are also using salicylates, these should be avoided in patients with varicella.

## TREATMENT

The only antiviral drug available in liquid formulation that is available for treatment of varicella for pediatric use is acyclovir. Given the safety profile of acyclovir and its demonstrated efficacy in the treatment of varicella, treatment of all children, adolescents, and adults with varicella is acceptable. Oral therapy with acyclovir (20 mg/kg/dose maximum: 800 mg/dose) given as four doses per day for 5 days can be used to treat uncomplicated varicella in individuals at increased risk for moderate-to-severe varicella, nonpregnant individuals older than 12 years of age and individuals older than 12 months of age with chronic cutaneous or pulmonary disorders; individuals receiving short-term, intermittent, or aerosolized corticosteroid therapy; individuals receiving long-term salicylate therapy; and possibly secondary cases among household contacts.

To be most effective, treatment should be initiated as early as possible, preferably within 24 hours of the onset of the exanthem. Valacyclovir (20 mg/kg/dose; maximum: 1,000 mg/dose administered three times daily for 5 days) is licensed for treatment of varicella in children 2 to more than 18 years of age, and both valacyclovir and famciclovir are approved for treatment of herpes roster in adults.

## Intravenous Therapy

Intravenous therapy is indicated for severe disease and for varicella in immunocompromised patients (even if begun more than 72 hours after the onset of rash). Any patient who has signs of disseminated VZV, including pneumonia, severe hepatitis, thrombocytopenia, or encephalitis should receive immediate treatment. IV acyclovir therapy (500 mg/m<sup>2</sup> q8h) initiated within 72 hours of development of initial symptoms decreases the likelihood of progressive varicella and visceral dissemination in high-risk patients.

Treatment is continued for 7–10 days or until no new lesions have appeared for 48 hours. Delaying antiviral treatment in high-risk individuals until it is obvious that prolonged new lesion formation is occurring is not advisable because visceral dissemination occurs during the same period.

Acyclovir-resistant VZV has been identified primarily in children infected with HIV.

These children may be treated with IV foscarnet (120 mg/kg/day divided q8h for up to 3 weeks). The dose should be modified in the presence of renal insufficiency. Resistance to foscarnet has been reported with prolonged use. Cidofovir is also useful in this situation. Because of the increased toxicity profile of foscarnet and cidofovir, these two drugs should be initiated in collaboration with an infectious disease specialist.

## PREVENTION

Varicella-zoster immune gamma globulin (VZIG) 125 U/kg (maximum: 625 U) may prevent in contact if administered 1 M within 96 hours of exposure. The groups who require protection are children under the age of 1 month, pregnant women, patients with leukemia and those on steroid therapy. Use of acyclovir as chemoprophylaxis is not recommended.

VZIG is available for postexposure prevention of varicella in high-risk susceptible persons. Post-exposure prophylaxis with acyclovir is effective when it is started at 8 or 9 days after exposure and is continued for 7 days.

The live-attenuated vaccine should be given as part of routine childhood immunization and “catch-up” immunization is recommended for all other susceptible children and adults. Varicella vaccine is also useful for postexposure prophylaxis when given within 3–5 days of the exposure.

## PROGNOSIS

Except for secondary bacterial infection, serious complications are rare and recovery complete in immunocompetent hosts. A live vaccine prepared with Oka strain is now available. The vaccine is given within 3 days of exposure, may prevent disease in more than 80% of individuals.

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# Whooping Cough

## PRESENTING COMPLAINTS

An 8-month-old girl was brought with the complaints of:

- Cough since 1½ months
- Congestion of face since 15 days
- Vomiting since 15 days
- Noisy respiration since 15 days

## History of Presenting Complaints

An 8-month-old girl was brought with history of episodes of paroxysm of the cough since 1 month. Mother complained that the child was having repeated episodes of cough. Each paroxysm of cough was followed by vomiting. Mother told that her child used to vomit ingested food material. It was associated with intense congestion of face and sometimes bluish coloration of face. Usually cough was associated with inspiratory sound.

## Past History of the Patient

She was the second child of nonconsanguineous marriage. She was born at full term by normal vaginal delivery. Child did not have any postnatal

significant event. She was discharged on the 4th day. She was exclusively on breastfeeds for first 4 months. Later weaning started gradually with cereals and fruits. There was no feeding problems. She was not immunized with pertussis component because of apprehension. Her elder sister was 3 years old and had intermittent cough for 3 weeks.

## EXAMINATION

The girl was moderately built and nourished. She was looking ill and mildly dehydrated. Anthropometric measurements included the length was 70 cm (75th centile), and the weight was 7 kg (50th centile). The head circumference was 42 cm.

She was afebrile, the pulse rate was 120 per minute, the respiratory rate was 32 per minute. Blood pressure recorded was 60/40 mm Hg. There was no pallor, no lymphadenopathy and no cyanosis.

Respiratory system revealed the presence of occasional crepitation on the right lung base. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 10.8 g/dL
TLC	: 18,200 cells/cu mm
DLC	: P <sub>40</sub> L <sub>56</sub> E <sub>3</sub> M <sub>1</sub>
ESR	: 8 mm in the 1st hour
AEC	: 334 cells/cu mm
Mantoux test	: Negative
X-ray chest	: Normal

## DISCUSSION

Pertussis is an acute, highly communicable infection of the respiratory tract caused by *Bordetella pertussis*. Children usually acquire the disease from symptomatic family contacts. The risk of the disease is highest under the age of 5 years. Regular immunization reduces the incidence and mortality of the pertussis.

Adults who have mild respiratory illness, not recognized as pertussis, frequently are the source

### CASE AT A GLANCE

#### Basic Findings

Length	: 70 cm (75th centile)
Weight	: 7 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 120 per minute
Respiratory rate	: 32 per minute
Blood pressure	: 60/40 mm Hg

#### Positive Findings

##### History

- Paroxysm of cough
- Whoop
- Vomiting
- Congestion

##### Examination

- Sick look
- Mild dehydration

##### Investigation

- ESR: Decreased
- Lymphocytosis

of infection. Asymptomatic carriage of *B. pertussis* is not recognized. Infectivity is greatest during the catarrhal and early paroxysmal cough stage (for about 4 weeks after onset).

Neither natural disease nor vaccination provides complete or lifelong immunity against pertussis reinfection or disease. Subclinical reinfection undoubtedly contributed significantly to immunity against disease ascribed previously to both vaccine and prior infection. The resurgence of pertussis has been attributed to a variety of factors, including partial control of pertussis leading to less continuous exposure, increased awareness, improved diagnostics, suboptimal vaccines, waning vaccine-induced immunity, and pathogen adaptation.

Protracted coughing (which in some cases is paroxysmal) can be caused by *Mycoplasma*, parainfluenza viruses, influenza viruses, enteroviruses, respiratory syncytial viruses, or adenoviruses.

Pertussis like illness is caused by adenovirus, *Bordetella parapertussis*, *B. bronchiseptica* and *Chlamydia*.

Active immunity follows natural pertussis. Reinfections occur years to decades later but are usually milder. Immunity following vaccinations wanes in 5–10 years.

## **PATHOGENESIS**

*Bordetella* organisms are small, fastidious, gram-negative coccobacilli that colonize only ciliated epithelium. The exact mechanism of disease symptomatology remains unknown. *Bordetella* species share a high degree of deoxyribonucleic acid (DNA) homology among virulence genes. *B. pertussis* produces numerous virulence factors, including toxins and attachment agents, many of which are antigenic and included in the acellular vaccine. The bacteria attach to ciliated epithelial cells of the respiratory tract, induce ciliary paralysis and local inflammation, and thicken and decrease clearance of secretions. Only *B. pertussis* expresses pertussis toxin (PT), the major virulence protein. PT has numerous proven biologic activities (e.g., histamine sensitivity, insulin secretion, leukocyte dysfunction).

These bacteria will multiply only in association with ciliated epithelium. They produce various active substances or virulent factors. These inflammatory debris accumulate in lumen of the bronchi. Bronchiolar obstruction and atelectasis result due to accumulation of mucus secretion. Pathological changes are also seen in brain and liver. Fatty infiltration of liver may be noted and cortical atrophy has been documented.

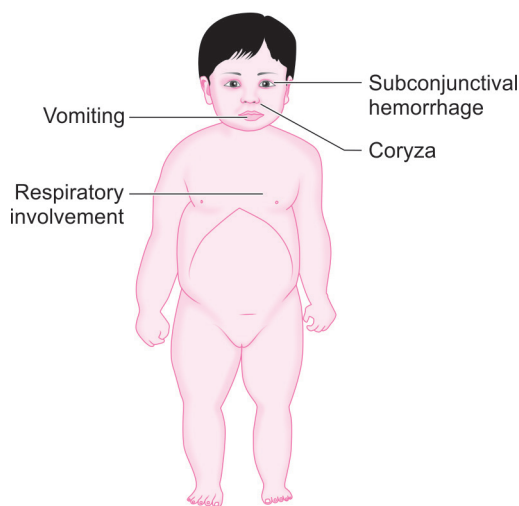
*B. pertussis* is not invasive. Pertussis toxin, necessary but not sufficient to cause clinical pertussis, is secreted by the bacteria and affects G-protein function, which prevents migration of lymphocytes to the area of infection, and inhibits the function of neutrophils, macrophages, monocytes, and lymphocytes. Adenylate cyclase toxin invades phagocytes and induces high levels of cyclic adenosine monophosphate (AMP), which impairs immune cell function and induces apoptosis.

Other cell-surface proteins, including filamentous hemagglutinin, pertactin, and fimbrial agglutinogens, are involved in bacterial attachment to ciliated respiratory epithelium. The function of additional factors, including tracheal cytotoxin, surface lipooligosaccharide, and cytoplasmic heat-labile toxin, is less well characterized. Communicability is highest early in the disease (catarrhal phase), but may persist for weeks in some individuals. Unrecognized disease serves as a reservoir to spread of infection.

## **CLINICAL FEATURES (FIG. 1)**

It is more infectious during catarrhal stage. The period may be considered to extend from the week after exposure to about 3 weeks after the onset of paroxysmal stage. It is spread mainly by droplet infection and direct contact.

Pertussis is extremely contagious, with attack rates as high as 100% in susceptible individuals exposed to aerosol droplets at close range. High airborne transmission rates were shown in pertussis despite vaccination with the acellular vaccine. *B. pertussis* does not survive for prolonged periods in the environment.



**Fig. 1:** Clinical features.

Chronic carriage by human is not documented. After intense exposure as in households, the rate of subclinical infection is as high as 80% in fully immunized or previously infected individuals. When carefully sought a symptomatic source case can be found for most patients.

The incubation period is 7–14 days but not more than 3 weeks. Clinically whooping cough has got three stages:

1. **Catarrhal stage:** This stage lasts for 10–14 days. The onset of pertussis is insidious, with catarrhal upper respiratory tract symptoms (rhinitis, sneezing and an irritating cough). Slight fever may be present; temperature greater than 38.3°C suggests bacterial superinfection or another cause of respiratory tract infection. The child has cough, coryza with nasopharyngeal secretion. The paroxysmal nature of cough can be suspected towards the latter part of this phase. The rapid succession of cough in an explosive manner. Child may appear choked, unable to breath.
2. **Paroxysmal stage:** This stage lasts for 2–4 weeks. After about 2 weeks, cough becomes paroxysmal, characterized by 10–30 forceful coughs terminates with a long drawn out inspiratory crowing sound or whoop. The paroxysm of cough terminates into vomiting. Whoop is produced by the air rushing during inspiration through the half open glottis. The whoop may not be present in neonate, where it is manifested with apnea and cyanotic spells. Paroxysm of cough are precipitated by food, cold air and liquid. Paroxysmal stage is considerably prolonged in young infants less than 3 months. Coughing is accompanied by cyanosis, sweating, prostration and exhaustion. This stage lasts for 2–4 weeks, with gradual improvement. Clinical pertussis is milder in immunized children. The bout of cough petechial and conjunctival hemorrhages are seen.
3. **Convalescent stage:** Vomiting becomes less severe. Appetite and general condition improve. This stage lasts for 2–4 weeks. Interval between the paroxysm of cough is prolonged. Severity of episodes decreases gradually. It is prolonged because of atelectasia, pneumonia and bronchiectasis. During the convalescent period, coughing in the young infant may actually become louder, although generally less distressing. Overall, the paroxysmal coughing gradually lessens in severity and frequency during convalescence. Paroxysms may disappear, only to reappear in a milder form during a subsequent respiratory illness

over the ensuing year. Persons with pertussis are considered infectious from onset of the catarrhal stage through the 3rd week of the paroxysmal stage or until 5 days after starting treatment.

Uncomplicated pertussis is usually an afebrile disease, so fever should prompt evaluation for a secondary bacterial infection. Otitis media and pneumonia are the most common secondary infections. Other pulmonary complications include atelectasis, emphysema, pneumothorax, and pulmonary hypertension.

Coughing and vomiting may result in esophageal tears with hematemesis and melena. Neurologic complications include hypoxic encephalopathy, seizures, and intracranial bleeds. Nutritional compromise and resultant failure to thrive are common in young infants recovering from pertussis.

Classic pertussis in the nonimmune host is difficult to confuse with other illnesses. In the immunized individual symptoms are less likely to be characteristic, a coughing illness for more than 2 weeks and/or posttussive emesis should arouse suspicion. In infants presenting with apnea, respiratory syncytial virus or other viral infection and serious bacterial illness need to be excluded.

*B. pertussis* is the cause of epidemic pertussis as well as of most sporadic pertussis. *B. paraptussis* may cause a similar syndrome that is less severe and of shorter duration. Protracted coughing illness mimicking pertussis may also be seen with adenovirus, *Mycoplasma*, and *Chlamydia*. Ancillary features of the illness such as sore throat, headache, or swollen lymph nodes, as well as knowledge of epidemiologically significant local pathogens, will aid diagnostically.

#### ESSENTIAL DIAGNOSTIC POINTS

- Cough coryza and fever
- Persistent staccato paroxysmal cough ending with high pitched inspiratory “whoop”
- Leukocytosis with absolute lymphocytosis
- Diagnosis is confirmed by fluorescent stain or culture of nasopharyngeal secretion

#### GENERAL FEATURES

- Cough
- Coryza
- Choking
- Whoop
- Decreased appetite
- Malnutrition
- Convulsions
- Hernia
- Rectal prolapse

Apnea and respiratory distress were the most frequent complications, followed by pneumonias. The frequency of complications declines with increasing age; however, posttussive emesis, protracted cough (>3 months) sleep disturbances, and weight loss are common in adults with pertussis; subcutaneous emphysema, pulled muscles and even broken ribs may occur in adults following paroxysmal coughing. The characteristic “whoop” is often absent in older individuals.

## DIAGNOSIS

Classical pertussis should be readily diagnosed based on clinical features. The presence of absolute peripheral lymphocytosis ( $>10,000$  lymphocytes/ $\mu\text{L}$ ) is supportive evidence for systemically active pertussis toxin. Absolute lymphocyte counts of more than  $20,000$  cells/ $\mu\text{L}$  are not uncommon, and total white blood cell counts more than  $100,000$  cells/ $\mu\text{L}$  have been reported.

A confirmed case is defined as one with any cough illness which *B. pertussis* is isolated and cultured, or a case with symptoms confirmed by polymerase chain reaction (PCR) or epidemiologic linkage to a laboratory-confirmed case.

Culture is considered the gold standard as it is the only 100% specific method for identification, specimen for culture is obtained by deep nasopharyngeal (NP) aspiration, and inoculation in Bordet-Gengou agar, Regan-Lowe or modified Stainer-Seholte media causes growth in 3–4 days. Recovery of organisms is highest during catarrhal and early paroxysmal stages. Previously immunized or antibiotic treated patients may produce a negative culture; however, this does not exclude the diagnosis of pertussis.

Blood and laryngeal swab cultures are incubated at  $35\text{--}37^\circ\text{C}$  in a humid environment and examined daily for 7 days for slow-growing, tiny, glistening colonies. Direct fluorescent antibody testing of potential isolates using specific antibody for *B. pertussis* and *B. parapertussis* maximizes recovery rates.

Identification of *B. pertussis* by culture or PCR from nasopharyngeal swabs or nasal wash specimens proves the diagnosis. PCR detection is replacing culture in some hospitals because of improved sensitivity, decreased time to diagnosis and cost. The organism may be found in the respiratory tract in diminishing numbers beginning in the catarrhal stage and ending about 2 weeks after the beginning of the paroxysmal stage.

PCR should be tested from nasopharyngeal specimens taken at 0–3 weeks following cough onset, but may provide accurate results for up to 4 weeks. The optimal timing for specimen

collection is 2–8 weeks following cough onset, when the antibody titers are at their highest; however, serology may be performed on specimens collected up to 12 weeks following cough onset.

After 4–5 weeks of symptoms, cultures and fluorescent antibody tests are almost always negative. Charcoal agar containing an antimicrobial should be inoculated as soon as possible. *B. pertussis* does not tolerate drying or prolonged transport.

Currently, the most generally accepted serologic criterion for diagnosis of pertussis is the use of an enzyme-linked immunosorbent assay to demonstrate a significant increase in immunoglobulin (Ig) G serum antibody concentrations against pertussis toxin between acute and convalescent specimens or a single point test collected 2–8 weeks following cough onset. Results may not correlate with clinical disease and can be difficult to interpret in a highly immunized population.

Enzyme-linked immunosorbent assays (ELISA) for detection of antibody to pertussis toxin or filamentous hemagglutinin may be useful for diagnosis but are currently not widely available and interpretation of antibody titers may be difficult in previously immunized patients.

The blood picture may resemble lymphocytic leukemia or leukemoid reactions. Fluorescent antibody staining of the laryngeal swab is a quick diagnostic test. ESR is reduced.

The chest X-ray reveals thickened bronchi and sometimes shows a shaggy heart border, indicating bronchopneumonia and patchy atelectasis.

Following natural infection, antibodies develop to several *B. pertussis* antigens. These responses do not confer lifetime immunity but rather wane in 7–20 years. Immunization with whole-cell vaccine likewise results in response to multiple antigens, but responses last only 6–12 years. The acellular pertussis vaccines are well tolerated, offer very targeted responses, but do not have durability of response. Recent outbreaks and increases in disease incidence suggest the protection afforded by acellular vaccines may be as short as 4–5 years.

### LABORATORY SALIENT FINDINGS

- Lymphocytosis
- Culture
- PCR reaction from nasopharyngeal swabs
- ELISA test
- Chest X-ray: Bronchopneumonia and patchy atelectasis

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pertussis includes bacterial tuberculosis, chlamydial and viral pneumonia. Cystic fibrosis and foreign body aspiration



may be considerations. Adenovirus and respiratory syncytial virus may cause paroxysmal coughing with an associated elevation of lymphocytes in the peripheral blood, mimicking pertussis.

- Foreign body
- Tuberculous lymph node
- Bronchiolitis
- Tracheitis
- Bronchiectasis

## COMPLICATIONS

The infants below 6 months have high maturity:

- Respiratory
  - Patchy atelectasis
  - Pneumonia
  - Interstitial pneumonia
  - Bronchiectasis
  - Subcutaneous emphysema
  - Pneumothorax
  - Flaring of tuberculosis
- Neurological
  - Resistant seizures
  - Ataxia
  - Intracranial hemorrhage
  - Aphasia
  - Hemiplegia
  - Paraplegia
- Gastrointestinal
  - Hernia
  - Rectal prolapse
  - Malnutrition

Bronchopneumonia due to superinfection is the most common serious complication. It is characterized by abrupt clinical deterioration during the paroxysmal stage, accompanied by high fever and sometimes a striking leukemoid reaction with a shift to predominantly polymorphonuclear neutrophils.

Atelectasis is a second common pulmonary complication. Atelectasis may be patchy or extensive and may shift rapidly to involve different areas of lung. Intercurrent viral respiratory infection is also a common complication and may provoke worsening or recurrence of paroxysmal coughing.

Otitis media is common residual chronic bronchiectasis is infrequent despite the severity of the illness.

Apnea and sudden death may occur during a particularly severe paroxysm. Seizures complicate 1.5% of cases and encephalopathy occurs in 0.1%. the encephalopathy frequently is fatal.

Anoxic brain damage, cerebral hemorrhage or pertussis neurotoxins are hypothesized, but anoxia is most likely the cause. Epistaxis and subconjunctival hemorrhages are common.

## TREATMENT

### Specific Measures

Treatment for clinical pertussis is primarily supportive. Hospitalization is indicated for all infants with severe paroxysms associated with cyanosis or apnea. Infants with potentially fatal pertussis may appear to be amazingly well between paroxysms. Caution should be exercised when suctioning these young, exhausted infants because it may precipitate a paroxysm.

Admission to an intensive care setting is indicated if emergent response to paroxysms cannot be managed on the ward. Supplemental oxygen, intravenous fluids, and nutritional support are frequently required in severe and protracted disease. Some have suggested that early extracorporeal membrane oxygenation with leukodepletion in the most severe cases may decrease mortality. Young infants should remain hospitalized until nutrition is adequate, no supportive intervention is required during paroxysms, disease is unchanged or improved for at least 48 hours, and the infant's care can be safely managed at home.

Antibiotic therapy has no discernible effect on the course of the illness once the paroxysms are well established; however, treatment may ameliorate disease expression for those who are treated in the catarrhal phase. Clinicians should strongly consider treating prior to test results if clinical history is strongly suggestive or patient is at risk for severe or complicated disease (e.g., infants).

All suspected and confirmed cases of pertussis should be treated in order to minimize secondary spread. The Centers for Disease Control and Prevention (CDC) recommends treating patients >1 year of age within 3 weeks of cough onset and those 1 year of age and pregnant = women within 6 weeks of cough onset. Treatment and post-exposure prophylaxis dosing is based on age and weight.

Infants younger than 3 months of age with suspected pertussis usually are admitted to hospital, as are many between 3 and 6 months of age unless witnessed paroxysms are not severe, as well as are patients of any age if significant complications occur.

Macrolides are the drugs of choice for the treatment of pertussis and may improve infant survival. Studies have demonstrated that both azithromycin and clarithromycin are as effective as erythromycin sulfate in eliminating B pertussis from the nasopharynx, although there are no data in infants younger than 1 month of age. Because of the known association of erythromycin

and infantile hypertrophic stenosis, it is not a preferred agent for use in neonates and should be used only if azithromycin is not available. There are data demonstrating that 7 days of erythromycin estolate are as effective as 14 days, which may reflect the improved penetration of this erythromycin formulation over others. Stomach upset is the most commonly reported side effect of erythromycin and frequently is a reason for patient noncompliance.

Antibiotics may ameliorate early infections but have no effect on clinical symptoms in the paroxysmal stage. Erythromycin is the drug of choice because it promptly terminates respiratory tract carriage of *B. pertussis*. A single resistant strain has been reported. Patients should be given erythromycin estolate (40–50 mg/kg/24 h in four divided doses for 14 days). Erythromycin ethylsuccinate is efficacious, but the higher dose recommended causes considerable gastrointestinal intolerance. A recent study suggests that 7 days and 14 days of treatment are equally effective. Clarithromycin for 7 days and azithromycin for 5 days were equal to erythromycin for 14 days in one small study.

Ampicillin (100 mg/kg/day in four divided doses) may also be used for erythromycin-intolerant patients. Household or other close contacts (e.g., in daycare centers) should be given erythromycin to reduce secondary transmission. This prophylaxis should be used regardless of age or immunization status.

Corticosteroids reduce the severity of disease but may mask signs of bacterial superinfection. Albuterol (0.3–0.5 mg/kg/day in four doses) has reduced the severity of illness, but tachycardia is common when the drugs are given orally and aerosol administration may precipitate paroxysms.

## General Measures

Nutritional support during the paroxysmal phase is important. Frequent small feedings, tube feeding or parenteral fluid supplementation may be needed. Minimizing stimuli that trigger paroxysms is probably the best way of controlling cough. In general, cough suppressants are of little benefit.

## Treatment of Complications

Respiratory insufficiency due to pneumonia or other pulmonary complications should be treated with oxygen and assisted ventilation if necessary. Convulsions are treated with oxygen and anticonvulsants. Bacterial pneumonia or otitis media requires additional antibiotics.

Antibiotics are given to shorten the course during catarrhal phase. Erythromycin is given in the dose of 40–50 mg/kg/day for 14 days. Small dose of bronchodilator may be helpful to relieve the spasms. Betamethasone 0.75 mg/kg/day may be helpful. Humidification of the air diminishes the viscosity of the mucus and child can bring it out more easily.

Pertussis vaccine should not be given to an infant with the history of convulsions associated with progressive neurological manifestation. This is to minimize the risk of encephalopathy following pertussis vaccine.

## PREVENTION

Active immunization with DTP vaccine should be given in early infancy. Acellular pertussis (DTaP) vaccines cause less fever and fewer local and febrile systemic reactions and have replaced the former whole cell vaccines. The recent increase in incidence of pertussis is primarily due to increased recognition of disease in adolescents and adults.

Chemoprophylaxis with erythromycin should be given to exposed family and hospital contacts, particularly those under age 2 years. Hospitalized children with pertussis should be isolated because of the great risk of transmission to patients and staff.

## PROGNOSIS

The prognosis for patients with pertussis has improved in recent years because of excellent nursing care, treatment of complications, attention to nutrition and modern intensive care. However, the disease is still very serious in infants under age 1 year; most deaths occur in this age group. Children with encephalopathy have a poor prognosis.

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# Birth Asphyxia

## PRESENTING COMPLAINTS

Newborn child was brought with the complaints of:

- Did not cry
- Flabby
- Not breathing

## History of Presenting Complaints

A multigravida mother aged about 28 years came to the labor room with delivery pain. This was her fourth pregnancy. There was history of delivery pain once in every 3 minutes. There was history of rupture of membrane about 1 hour back. Amniotic fluid was clear. Over the next 4 hours she delivered spontaneously by vertex presentation. The duration of the second stage of delivery was 10 minutes.

Female child was born. Child did not cry immediately after the delivery. Child was in the

state of limp and apneic. Apgar score at 1 minute was 2/10. Head is positioned and airway was cleared. Respiration is assessed. Child was dried and suctioning was done. Oxygen was given. Child started having spontaneous breathing. Oxygen was on flow at the rate of 4 L to maintain satisfactory oxygen saturation. Child became pink, tone became hypertonic and started to cry. The heart rate came to normal. Apgar score at 5 minutes was 8/10. Child was later shifted to neonatal intensive care unit (NICU) for further management.

## EXAMINATION

The newborn baby was moderately built and nourished. Child was limp and apneic. Child was not breathing spontaneously. Child was flabby. Child was not crying even to the little stimulation on the back and sole. Child was completely cyanosed.

The anthropometric measurements included, the weight was 2.5 kg (3rd centile), the length of the baby was 48 cm (10th centile). The head circumference recorded was 33 cm. The gestational age corresponds to 36 weeks.

Newborn was afebrile. The heart rate was 86 per minute. Child was not spontaneously breathing. Blood pressure recorded was 50/30 mm Hg. Baby looked pale, cyanosis was present. There was no edema, no lymphadenopathy. Respiratory system revealed no breath sounds in the beginning. Later after suctioning and oxygen, breath sounds were heard at both bases. Crepitations were present. Cardiovascular system revealed bradycardia in the beginning and later it became normal. Per abdomen examination was normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 13,600 cells/cu mm
DC	: $P_{78} L_{18} E_2 B_2$
Blood glucose	: 56 g/dL
PCV	: 45%

### CASE AT A GLANCE

#### Basic Findings

Length	: 48 cm (10th centile)
Weight	: 2.5 kg (3rd centile)
Temperature	: 37°C
Pulse rate	: 86 per minute
Respiratory rate	: No spontaneous breathing
Blood pressure	: 50/30 mm Hg

#### Positive Findings

##### History

- Multigravida
- Fast delivery
- No spontaneous breathing
- Apneic and limp

##### Examination

- Limp and apneic
- No spontaneous breathing
- Cyanosis
- Bradycardia
- Bilateral basal crepitation

##### Investigation

- ABG: Acidotic feature

Blood group and Rh typing	: A positive
BUN	: 20 mg/dL
Serum creatinine	: 1 mg/dL
Serum electrolyte	: Na—107 mEq/L K—4 mEq/L Cl—80 mEq/L
ABG	: pH < 7 mm Hg PaCO <sub>2</sub> 60 mm Hg PaO <sub>2</sub> : 40 mm Hg
Chest X-ray	: NAD
Blood culture	: Sterile
Swab culture—ear and throat	: Sterile

## DISCUSSION

Birth asphyxia is a clinical condition, where in the cell is deprived of oxygen and carbon dioxide gets accumulated in the tissue. It is the most common medical emergency in newborn infants. It is the leading cause of neonatal mortality and morbidity. To prevent this, adequate ventilation and proper circulation should be established.

After the birth, the lungs expand as they are filled with air. The fetal lung fluid gradually leaves the alveoli. One-third of the fetal lung fluid is removed during vaginal delivery as the chest is squeezed, the lung fluid comes through the nose and mouth. The first few breaths are very powerful. This helps in expanding alveoli and replaces the lung fluid with air. The first breath is usually followed by a cry. This enables the infant to breathe out against the closed glottis. This produces positive intrathoracic pressure up to 40 cmH<sub>2</sub>O. Functional residual capacity (FRC) reaches about 75% of the final aeration.

The first functional breath is stimulated by many factors:

*Physiological hypoxia:* This is present at birth. Average volume of oxygen saturation of arterial blood is 22%. pCO<sub>2</sub> level 60 torr, pH is 7.28. This stimulates carotid and aortic receptors.

*Clamping of the cord:* This increases arterial pressure. This in turn stimulates aortic baroreceptors and sympathetic nervous system.

*Sudden cooling of the body:* This acts through the trigeminal cold receptors.

Infant should breathe spontaneously after delivery. In about 6% of delivery cases, infants require some intervention, immediately after the birth. This intervention is more common among very low birth weight babies. Seventy percent of the infants requiring resuscitation come under

high-risk pregnancy. Hence, high-risk pregnancy should always be attended by pediatrician.

Full-term mature infants delivered normally, will breathe within few seconds. The time interval between the delivery of nose till the first breath is about 20–30 seconds. Child will have rhythmic respiration within 90 seconds.

Fetal lungs contain fluid. They do not contain oxygen. Blood flow through the lungs is markedly diminished, following birth. This is due to partial closing of arteries in lungs. This results in a large amount of blood being directed away from the lungs to ductus arteriosus.

High-risk pregnancies are anticipated with certain problems. For development of spontaneous breathing, these pregnancies should be attended by pediatrician. These include meconium-stained liquor, breech delivery, assisted delivery, abnormal fetus, postdated pregnancy, maternal hypertension, Rh incompatibility, maternal diabetes, preterm delivery and young or elderly primi.

## PATHOPHYSIOLOGY OF ASPHYXIA

A rational approach to resuscitation must be based on the physiologic changes in the circulatory and respiratory systems that occur normally as the newborn infant adapts to extrauterine life.

The human infant is particularly vulnerable to asphyxia in the perinatal period. During normal labor, transient hypoxemia occurs with uterine contractions, but the healthy fetus tolerates this well. There are five basic causes of asphyxia during labor and delivery:

1. Interruption of the umbilical blood flow (e.g., cord compression)
2. Failure of gas exchange across the placenta (e.g., placental abruption)
3. Inadequate perfusion of the maternal side of the placenta (e.g., severe maternal hypotension)
4. An otherwise compromised fetus who cannot further tolerate the transient, intermittent hypoxia of normal labor (e.g., the anemic or growth retarded fetus)
5. Failure to inflate the lungs and complete the change in ventilation and lung perfusion that must occur at birth.

Asphyxia in the fetus or newborn infant is a progressive and reversible process. The speed and extent of progression are highly variable. Sudden, severe asphyxia can be lethal in less than 10 minutes. Mild asphyxia may progressively worsen over 30 minutes or more. Repeated episodes of brief, mild asphyxia may reverse

spontaneously but produce a cumulative effect of progressive asphyxia. In the early stages, asphyxia usually reverses spontaneously if its cause is removed. Once asphyxia is severe, spontaneous reversal is unlikely because of the circulatory and neurologic changes that accompany it (**Fig. 1**).

Cardiac output is maintained early in asphyxia, but its distribution changes radically. Selective regional vasoconstriction reduces blood flow to less vital organs and tissues such as gut, kidneys, muscle and skin. Blood flow to the brain and myocardium increases, thereby maintaining adequate oxygen delivery despite reduced oxygen content of the arterial blood. Other organs and tissues must depend on increased oxygen extraction to maintain oxygen consumption. Pulmonary blood flow is low in the fetus. It is decreased further by hypoxia and acidosis. As a consequence of these adaptations, fetal oxygen consumption decreases.

Early in asphyxia, newborns make vigorous attempts to inflate their lungs. If successful, the lungs become adequately ventilated and perfused, but the mere presence of gasping does not ensure that this will happen. As asphyxia becomes more severe, the respiratory center is depressed, and the chances of an infant spontaneously establishing effective ventilation and pulmonary perfusion diminish.

If asphyxia progresses to the severe stage, oxygen delivery to the brain and heart decreases. The myocardium then uses its stored reserve of glycogen for energy. Eventually, the glycogen reserve is consumed and the myocardium is exposed simultaneously to progressively lower values of  $pO_2$  and pH. The combined effects of

hypoxia and acidosis lead to decreased myocardial function and decreased blood flow to the vital organs. Brain injury begins late during this phase.

Hypoxia in newborn can be:

- *Intrauterine*: It is manifested by abnormal fetal heart rate pattern, fresh meconium and reduced fetal movements. It may be acute, chronic or acute on chronic.
- *Intrapartum*: It may be acute, acute on chronic due to placental insufficiency. This may be also the cause of prolonged labor due to oxytocin infusion or cord compression. It implies fetal bradycardia and hypoxemia. This may lead to metabolic acidosis.

#### GENERAL FEATURES

- No breathing
- Apnea
- Mottling

### CAUSES OF ASPHYXIA

#### Maternal

- Sedation
- Hypertension
- Eclampsia
- Acute hypotension
- Maternal diabetes
- Age less than 15 years and more than 35 years

#### Fetal

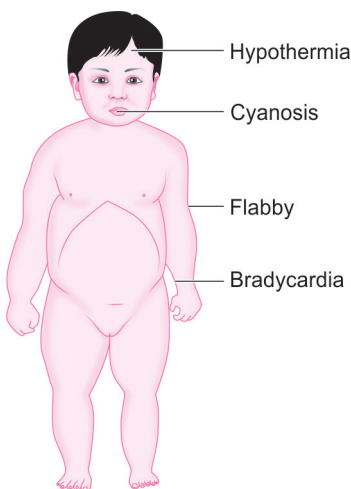
- Malpresentation
- Cephalopelvic disproportion
- Multiple birth
- Premature
- Postmature
- Hydrops

#### Placental

- Abruption placenta
- Placenta previa
- Cord prolapse
- Twin-to-twin transfusion
- Bleeding into the mother

There are many situations which cause the delayed onset of respiration other than asphyxia. These include:

- Drugs
  - Depressing the central nervous system
  - Pethidine 4 hours before delivery
- Trauma to central nervous system (CNS)
- Prematurity
- Anemia
- Congenital malformation



**Fig. 1:** Clinical features.



## Delivery

### *Delivery room resuscitation of the newborn infant:*

The presence of certain antepartum, intrapartum, or postpartum risk factors predicts many but certainly not all infants who require help in the delivery room. Premature infants, when compared to term infants, are at particular risk for a difficult transition following birth. The most common contributing factor for infants in need of resuscitation is asphyxia. Asphyxia results in concomitant hypoxia and hypercapnia and causes a mixed metabolic and respiratory acidosis. The asphyxia can result from either failure of placental gas exchange before birth or deficient pulmonary gas exchange once the newborn is delivered.

The following equipment should always be immediately available: functional positive pressure ventilation device capable of delivering oxygen, suction devices (bulb syringe as well as wall suction and suction catheters), a functional laryngoscope with appropriate-sized blades, and appropriate endotracheal tubes. Pulse oximetry monitoring should be available for every delivery. Cardiac monitoring may help to monitor infants receiving positive pressure ventilation and is recommended if cardiac compressions are initiated. In certain potentially dire circumstances, an umbilical venous line should be prepared and resuscitation medications drawn up and labeled for potential use.

Resuscitation of the child requires rapid and systematic response that is well rehearsed. A team approach works better, in which each member should take the responsibilities. The leader should identify the problem and direct the personnel. The intervention should begin instantly.

The main principle of the resuscitation is to assist the infant in establishing adequate ventilation, pulmonary perfusion and adequate cardiac output. Other supportive and important care includes adequate peripheral circulation, maintaining blood sugar level, electrolyte balance, prevention of heat loss. The cause of the cardio-respiratory problem should be corrected.

Immediately after delivery of the head, but prior to first breath, the infants' nose and mouth should be gently suctioned. The infant is then delivered and umbilical cord is clamped and cut. Neonate should be kept on their side with neck in neutral position. Care should be taken to prevent hyperextension or underextension of the neck, since either of these may decrease air entry.

Delayed cord clamping (DCC) after birth provides transfusion of placental blood to the newly

born infant. In full-term infants, the placental blood volume at birth is approximately 35 mL/kg of birth weight. If the infant is held at the level of the introitus after birth, 40% of this blood volume will be transferred to the infant within 1 minute after birth. In full-term infants, DCC improves hemoglobin levels at birth and iron stores throughout infancy. The only known negative outcome of DCC is hyperbilirubinemia, leading to increased need for phototherapy. In preterm infants, DCC improves short-term outcomes. For example, it reduces the need for blood transfusion and reduces intraventricular hemorrhage (all grades) and necrotizing enterocolitis. Based on the available data, DCC should be performed in preterm and term infants who do not require resuscitation at birth.

Infant is transferred to prewarmed towel or blanket. It is very important to keep the baby warm. Baby should be quickly dried and wrapped in a warm blanket to prevent heat loss from evaporation. Hypothermia increases the metabolic rate and oxygen consumption. This causes acidosis, hypoglycemia and predisposes coagulation abnormalities. If the infant is preterm, place the infant on a portable, chemically-activated heating pad under a layer of warm blankets. If the baby is less than 32 weeks estimated gestational age, place the trunk and extremities into a food-grade resealable polyethylene bag or plastic wrap.

Next, clear the airway. Gently suction the oropharynx and nose. If the infant's respiration is vigorous, nothing more may be necessary. Attach ECG electrodes and pulse oximeter, monitor the heart rate and oxygen saturations. The infant should be placed with the neck in mild extension so that the airway is maximally patent. Sometime shoulder roll helps to maintain correct position of the head. If the airway is obstructed or positive pressure ventilation is required secretions should be gently suctioned from the mouth and then nose with a bulb syringe or suction catheter. Take care to avoid vigorous or deep suction because it can cause vagal stimulation with apnea and bradycardia.

Both drying and suctioning are forms of the tactile stimulation. These are sufficient to initiate and support respiration. An infant in primary apnea will respond to almost any form of stimulation. But, however, the baby remains apneic, gasping, or with an inadequate heart rate, the infant is in secondary apnea, and effective positive pressure ventilation must be initiated without delay. If the infant is not breathing or has inadequate respiratory effort, brief tactile stimulation either by rubbing the back or by slapping/flicking the soles

of the feet. If the infant does not respond within few seconds, positive pressure ventilation should be initiated promptly. Gentle rubbing of the trunk or extremities may help rate and depth of respiration once the breathing has been established.

Process of evaluation and resuscitation begin as soon as child is born. Mouth, oropharynx and nose are thoroughly suctioned. This helps to keep airway patent. If the thick meconium is present, aspiration is done directly from the trachea, after intubation. In the meanwhile, Apgar scoring is done to assess the status of the baby.

### Apgar Scoring

Virginia Apgar was an anesthetist, who tabulated scoring to assess the infants response to stress of the labor and delivery. It consists of total points assigned to the five objective signs in the newborn. The signs are evaluated and scoring is done. Unusually the scoring is done at 1 minute and 5 minutes, and updated every 5 minutes until it is normal.

Sign	0	1	2
Appearance	Pale or blue	Peripheral cyanosis	Pink
Pulse rate	No	<100	>100
Grimace	No	Examine	Cry
Activity	Flaccid	In between	Flexed
Respiration	No	Slow and gasping	Crying

### Inference

Apgar score	Inference
8–10	No asphyxia
5–7	Mild asphyxia
3–4	Moderate asphyxia
0–3	Severe asphyxia

Because of practical limitation of Apgar scoring action-oriented assessment is done. This offers immediate therapeutic guide for the management.

#### Action-oriented assessment:

1. *Fetal distress:* Yes/No
2. *Medication:* Yes/No
3. *First cry:* Minutes after the births
4. *Respiration:* Absent/slow/irregular/crying
5. *Heart rate:* Absent/up to 100/more than 100

### Steps in Resuscitation

- If 1 minute Apgar score is 5–7, i.e., mild asphyxia, baby requires to be administered oxygen with bag and mask.

- If 1 minute Apgar score is 3–4—moderate asphyxia, oxygen is administered by bag and mask. If spontaneous breathing is not established and if there is history of pethidine administration, naloxone is given in the dose of 0.1 mg/kg. Simultaneously heart rate is evaluated.
- If 1 minute Apgar score is 0–2—severe asphyxia. Here failure of bag and mask requires prompt intubation to establish respiration. Size of the endotracheal tube is decided depending upon the weight of the child.

*1 minute Apgar:* It correlates with umbilical cord pH. It is an index of intrapartum asphyxia. In very low birth weight babies, Apgar may not indicate severity of asphyxia.

*Apgar score beyond 1 minute:* This reflexes child's changing conditions and response to resuscitation efforts. Low Apgar score indicates further therapeutic effects. Apgar score of 3 or less is likely to be associated with long-term neurological regulate. By this time child can be clinically classified, and action can be started promptly. The clinical classification can be done as:

- Vigorous crying
- Pale apneic and bradycardia
- Gasping and bradycardia
- Asystole but potentially revivable
- Stillborn or macerated

However, some infants with severe acidosis have normal Apgar scores, and with some normal blood gases and pH have very low scores. Maternal anesthetics, sedatives, maternal drugs, fetal sepsis and CNS pathologic conditions can lower the Apgar score; extremely premature infants often have low scores without any other evidence of asphyxia. Regardless of the cause, an Apgar score that remains low calls for action. The clinical significance of the Apgar score increases with time. Scoring should continue every 5 minutes until the score increases to 7 or above. The length of time it takes to reach a score 7 is a rough indication of severity of asphyxia.

### Indications for Resuscitation

Infants with poor, gasping, or absent respiratory effort: with inadequate heart rate below 100 bpm; or who are born preterm should be taken to the radiant warmer for further assessment and possible resuscitation interventions. Heart rate may initially be assessed by listening to the precordium with a stethoscope but cardiac monitoring can be used at any time as well. Palpation of the base of the cord

should not be performed as this is not accurate. Gasping, apnea, and a heart rate below 100 bpm are signs that indicate the need to clear the airway and provide positive pressure ventilation.

Infant weight (g)	Size of the tube (Internal diameter)
<1000	2 mm
1000–2000	2.5 mm
2000–3000	3 mm
>3000	3.5 mm

## Modalities of Intervention

Once the neonate is assessed, the mode of intervention should be clear. There are few modes of intervention as given below:

Modalities of intervention:

- No further action
- Suctioning
- Oxygen
- Bag and mask
- Intubation
- External cardiac massage

### No Further Action

Here the baby is crying lustily. The heart rate and the respiratory rate are good. No resuscitation is required, cord is clamped, vitamin K is given. Baby is given to the mother.

### Suctioning

This should be gentle suction. Large amount of secretion is found in the mouth and pharynx. Gentle oropharynx and nasal nares suctioning is done. This will also act as stimulus but should be done carefully. Catheter size number 8F or 10F should be used. Suctioning should not be continued for more than 5 seconds. This should be accompanied by monitoring heart rate. Deep and longer duration suctioning at oropharynx produces bradycardia and apnea.

If there are evidences of meconium staining, thorough suctioning of the mouth, nose and posterior pharynx should be performed soon after the delivery of the head. If the meconium is thick and child is depressed, direct endotracheal tube suction should be done. Tracheal suctioning should be repeated until no further meconium can be aspirated.

Infant is positioned in supine. A small roll of towel is kept under the shoulders in order to extend the neck and open the airways. Suctioning of the oral cavity, hypopharynx and nose is done.

The mask should be tightly fit on the face enclosing nose and mouth of the baby. This should not injure eye and other facial structures. The oxygen reservoir should be attached to the bag to increase the concentration of oxygen delivered to the baby.

### Facial Oxygen

In utero, the oxygen tension of the fetus is relatively low compared to adult levels. Healthy term newborns take 5–10 minutes for preductal oxygen saturations to reach 90% without intervention. In term infants, resuscitation should be initiated with 21% fraction of inspired oxygen ( $\text{FiO}_2$ ) and the oxygen subsequently adjusted to meet normal oxygen saturation goals per minute of life for healthy term infants.

Oxygen use during resuscitation of preterm infants remains controversial. Preterm infants are often hypoxemic due to lung immaturity and impaired gas exchange. However, they are also deficient in antioxidant protection and thus face potential adverse effects from exposing developing organs to high concentrations of inspired oxygen or high blood oxygen tension.

For all infants who require respiratory support or supplemental oxygen during resuscitation, pulse oximetry should target oxygen saturations based on published nomograms of preductal oxygen saturations during the first 10 minutes of life.

This is indicated when there is cyanosis. Here child may be breathing spontaneously with normal heart rate, but child may be slight cyanotic. Oxygen is given at the rate of 5 L/min. It is quite safe administer 80% oxygen.

### Bag and Mask (Table 1)

Hundred percent oxygen is provided during bag and mask ventilation. The life hand is used to hold the mask to baby's face while the right hand squeezes the bag. Little or ring fingers of the left hand is placed under the baby's chin and neck is slightly extended. This prevents the head from moving around and maintain as open airway. With other fingers and thumb, mask is firmly placed to ensure tight seal. Tight seal is confirmed by the characteristic rasping noise when the bag is squeezed only the thumb and two fingers is used to squeeze the bag. Bag should be squeezed gently to depress few centimeters. The rate should be maintained at 40–60/min.

If the child is gasping and taking shallow breathing and is bradycardiac, then ventilation is achieved by using bag and mask.

**TABLE 1:** Types of positive ventilation devices for the newborn.

Characteristic	Self-inflating bag	Flow-inflating	T-piece resuscitator
Appropriate-sized masks	Available	Available	Available
Oxygen concentration	Only with reservoir	Yes	Yes
90–100% capability	Only with blender plus reservoir	Only with blender	Only with blender
Variable concentration	40% O <sub>2</sub> delivered with no reservoir attached		
Peak inspiratory pressure	Amount of squeeze measured by pressure gauge	Amount of squeeze measured by pressure gauge	Peak inspiratory pressure determined by adjustable mechanical setting
PEEP	No direct control (unless optional PEEP valve attached)	Flow control valve adjustment	PEEP control
Inspiratory time	Duration of squeeze	Duration of squeeze	Duration that PEEP cap is occluded
Appropriate sized bag	Available	Available	Available
Safety features	Pop off valve Optional pressure gauge	Pressure gauge	Maximum pressure relief valve Pressure gauge

*Indications for bag and mask:*

- Apnea unresponsive to suctioning and gentle stimulation
- Heart rate less than 100 per minute
- Persistent central cyanosis with 100% oxygen
- Gasping respiration

Primary mechanism is the initiation of spontaneous breathing due to head paradoxical reflex. Rapid inflation of the lungs causes the baby to take an inspiration, which is followed by the gasps and then normal breathing.

Effective ventilation of the lungs is the most critical step in stabilization of the newborn infant who is not transitioning well at birth.

Three different devices (self-inflating bag, flow-inflating bag, and T-piece resuscitator) are currently available for ventilation of the newborn in the delivery room, each with its particular positive and negative features.

Ventilation can be provided via an appropriately sized face mask, laryngeal mask, or endotracheal tube. In order to provide effective ventilation via face mask, the first step is to make sure the infant is maintained in the open airway position. The mask must be appropriately sized to achieve a good seal. It should fit snugly around the mouth, supported by the chin and bridge of nose. The mask should not rest on the eyes because adequate pressure to achieve an adequate seal often elicits an adverse vagal reflex. Lack of appropriate airway position and poor seal are common causes of inadequate ventilation and resultant poor response to positive pressure ventilation in the delivery room. The best

sign that effective ventilation is underway is a rapid rise in heart rate, followed by improvement in oxygen saturation and tone. If there is not rapid improvement, then look for the presence of chest rise with each ventilation and listen for breath sounds.

Ventilation rates of 40–60 breaths per minute are recommended. If it is easy for an inexperienced provider to deliver much higher rates than are beneficial, so counting out loud, to maintain a steady rhythm of one breath per second can be helpful. Initial-inflation pressures may be high to inflate the lungs, but having done so, adjust the inspiratory pressure to maintain a heart rate greater than 100 beats per minute avoiding overdistingending the lungs. The optimum inspiratory pressure, inflation time, and flow rate required to maintain effective ventilation varies. If the heart rate (>100 bpm), oxygen saturations, and tone improve, and the baby begins to breathe spontaneously, then the bagging rate can be gradually reduced. The stomach should be decompressed to prevent gas distention and aspiration of stomach contents (which can further impede effective ventilation) via placement of an orogastric tube if prolonged bagging is needed.

If the chest expansion is inadequate, the following steps are to be taken (a) reapply the mask, (b) reposition the head, (c) remove the secretion from the mouth, (d) open the infant's mouth slightly, (e) ventilate with larger pressures.

The inflation pressure should be around 30–40 cmH<sub>2</sub>O for 1 second. This should be

adequate enough to expand the lung. This should be given at the rate 40/min. In an apneic child, the pressure should be around 40 cmH<sub>2</sub>O. The inspiration and expiration ratio should be around 1:1. To maintain the maximum residual capacity, lungs should be kept inflated for 3 seconds. In an apnea, gradual inflation of the lungs to a peak pressure of 40 cmH<sub>2</sub>O over 3.5 seconds once or twice is best.

Bag and mask ventilation may produce gastric distension. This will compromise diaphragmatic movements. It may be necessary to decompress the stomach with a nasogastric tube.

Bag and mask ventilation can be stopped, if the neonate resumes normal respiration and heart rate remains above 100 per minute. Otherwise it should be continued and cardiac compression should be provided.

Three signs indicate improvement include (i) increasing heart rate, (ii) spontaneous respiration, (iii) improving color.

### Intubation

Intubation may be performed for a variety of indications during resuscitation. These include suctioning an obstructed airway, inadequate response and/or poor chest rise during bag-mask ventilation, need for positive pressure ventilation beyond a few minutes, need for external chest compressions, endotracheal delivery of epinephrine if the intravenous route is inaccessible, surfactant administration, and suspected diaphragmatic hernia.

*Laryngoscope blade size, endotracheal tube (ETT) size, depth of insertion for babies of various estimated gestational ages (EGAs).*

Blade size	ETT size (mm)	EGA (weeks)	Depth of insertion (cm)
No. 0 or No. 00	2.5	23–24	5.5
No. 0 or No. 00	2.5	25–26	6.0
No. 0	2.5–3.0	27–29	6.5
No. 0	3.0	30–34	7.0–7.5
No. 1	3.5	34–38	8.0–8.5
No. 1	3.5–4.0	>38	9.0–10.0

This is indicated in terminal apnea. The state is diagnosed in a child who is pale or even white. Child is completely limp and makes no effort at all to breathe. Child is bradycardiac, i.e., 80 per minute and asystole. The child who is under 32 weeks of gestation and who is not breathing

well should be intubated quickly. Elective intubation should be given to those who are under 28 weeks of gestational maturity.

For endotracheal tube size, laryngoscope blade size, and depth of insertion. Use of a stylet is an option as long as care is taken that the tip does not protrude beyond the tube and it is secured so that accidental trauma does not occur. Intubation is a skill that takes practice. An increasing heart rate and end-tidal carbon dioxide detection after several breaths are the primary methods of confirming ventilation.

Infant is positioned with the neck slightly extended. Free-flow oxygen is provided during the procedure. Laryngoscope is held with the left hand, mouth is opened with right index finger, the blade is inserted under the tongue. Laryngoscope blade is lifted upward and forward so that blade is parallel to infants body. Epiglottis, vocal cords and glottis are visualized. If the esophagus is seen, the laryngoscope is withdrawn until epiglottis is seen. If the tongue is seen, the laryngoscope is advanced until it enters the vallecula or passes under epiglottis. Gentle pressure is provided over the cricoid cartilage of the trachea. Slightly curved endotracheal tube is inserted through a C-shaped arch. Tube is passed into the mouth at right corner. The visualization of the glottis is maintained. Tip of the tube passes through the vocal cord. The best location for endotracheal tube is mid way between glottis and carina.

Intubation attempt should be limited to 20 seconds. Bag and mask ventilation should be done if the attempt is unsuccessful. Endotracheal tube position is confirmed by auscultation and chest wall movements.

The key point in the intubation is the correct position of the laryngoscope and position of the baby. Baby's chin sternum and genitalia are lined up in single plane. Laryngoscope and blade are placed in that angle. Then intubator can see the anatomical landmarks like posterior tongue, epiglottis, larynx and esophagus. Then intubator can make adjustment in position of the blade and can locate the vocal cords.

The most common sign that ETT is not in the trachea is that the child is not becoming pink and remain bradycardiac. Additional indications are lack of any chest movements, unequal chest movements and abdominal distension. Listening with the stethoscope can be misleading especially in a small child as the breath sounds are easily transmitted to the lungs even though the tube is in esophagus.



Either measure the distance from the septum of the nose to the tragus of the ear and add 1 cm for tube insertion depth, or use the gestational age-based depth of insertion table. Secondary confirmation includes seeing chest rise after beginning positive pressure breaths through the tube, listening for equal breath sounds, and seeing condensation within the tube. Subsequent radiographic confirmation of proper placement is needed. Prolonged or repetitive intubation attempts should be interrupted for reapplication of bag mask ventilation to avoid exacerbation of hypoxia and hypoventilation.

### *External Cardiac Massage*

Chest compression consists of rhythmic compression of sternum pressing the heart against the spine. It results in the rise of intrathoracic pressure and circulation of blood to the vital body organs.

The heart circulates blood throughout the body and delivers oxygen to the vital organs. When the infant becomes hypoxic, heart rate slows and myocardial contractility decreases. That compression are used to increase circulation and oxygen delivery. It should be accompanied by ventilation with 100% oxygen.

If even after intubation for 15–30 seconds and with 100% oxygen the heart rate remains low, i.e., 60 per minute, cardiac massage should be done.

Current resuscitation guidelines recommend cardiac compressions for a newborn infant with a heart rate below 60 bpm despite adequate ventilation with supplementary oxygen for 30 seconds. Because ventilation is the most effective action in newborn resuscitation and because chest compressions are likely to interfere with effective ventilation, resuscitation providers are strongly encouraged to optimize assisted ventilation via endotracheal tube before initiating chest compressions. Once compressions are initiated, the oxygen concentration should be increased to 100%.

Chest compression should be given to a depth of approximately one-third the anteroposterior diameter of the chest. Back support should be provided by the tips of the encircling finger in two-thumb method or by the second hand being placed in the two-finger method compression coordinated, with the ventilation should be continued until the heart rate is greater than 60 beats per minute.

The best technique is to stand at the foot end of the infant. Both the thumbs are placed one above the other at the junction of middle and lower third of the sternum. The remaining fingers of both the

hands are wrapped around the chest supporting the back.

In the other technique, sternum is compressed by using two fingers, ring and middle finger. The fingers are placed about 2 cm below the nipple line. In spite of all these maneuvers, if the child is not reviving then the following condition should be thought off.

Compression is done at the rate of 90 per minute. One ventilation should follow every third chest compression. Thus, in 1 minute 90 chest compression and 30 positive pressure breath should be given in the ratio of 3:1. Carotid and femoral pulse are checked to know the effectiveness of compression. If the heart rate is more than 60 per minute, chest compression is stopped, but the ventilation should be continued till the heart rate reaches 100 per minute and infant is breathing spontaneously.

If the heart rate is less than 60 per minute, chest compression bag and mask ventilation is continued and medication are started.

The goal of cardiac compressions is to perfuse the heart and the brain. If severe asphyxia results in asystole or agonal bradycardia, the newborn myocardium is depleted of energy substrate. Adequate coronary perfusion must be re-established with oxygenated blood in order to regenerate sufficient adenosine 5-triphosphate required for effective myocardial function and return of spontaneous circulation.

Coronary perfusion pressure is the difference between the aortic diastolic blood pressure and the right atrial end-diastolic blood pressure. Thus, cardiac compressions and adequate systemic vascular resistance are needed to generate an adequate diastolic blood pressure in order to achieve return of spontaneous circulation. Given the profound vasodilation that typically results from the significant acidemia induced by asphyxia, a vasopressor agent such as epinephrine will frequently be required to achieve an adequate aortic diastolic pressure for sufficient coronary perfusion.

Conditions not responding to resuscitation procedure:

- Tension pneumothorax
- Prematurity
- Cardiac anomalies
- Pulmonary hypoplasia
- Diaphragmatic hernia

### **Use of Drugs**

If the baby is apneic despite of intubation and ventilation and is requiring external cardiac

massage for asystole or severe bradycardia then the drugs are necessary.

### Routes of Administration

**Intratracheal:** This route is excellent for administration of adrenaline and atropine. It can be used immediately and lungs absorb immediately. The dose is double the intravenous dose. Drugs should be diluted with 2 mL of normal saline and then injected along the endotracheal tube. Ventilation is then reconnected, which ensures the drug to reach the lung.

**Intravenous:** Central venous line is used.

**Intracardiac:** This is extremely hazardous as it is easy to puncture the lungs or rupture the coronary artery. The drugs do not work any better just because they are in the heart.

Umbilical vein provides ready venous access. A loose tie of the umbilical tape is tied around the base of the cord. French catheter of 3.5–5 size is flushed with normal saline. Umbilical cord is cut with a sterile scalpel about 1–2 cm from the base. A large thin walled umbilical vein is identified. Umbilical catheter is inserted into the vein until free flow of the blood is aspirated. This should be only few centimeters into the vein. Catheter is then connected to stop clock. This helps to administer the medicine and normal saline flush.

### Drugs and Dosages

**Epinephrine:** Although based primarily on adult and animal studies, epinephrine has long been the preferred vasopressor agent for treatment of ventilation-resistant neonatal cardiac arrest. The most important action of epinephrine is to stimulate  $\alpha$ -adrenergic receptor-mediated vasoconstriction in order to elevate the diastolic blood pressure and thus the coronary perfusion pressure. Consequently, during neonatal cardiac arrest, if effective ventilation and cardiac compressions have failed to re-establish perfusion, epinephrine should be given rapidly. Current guidelines recommend that if agonal bradycardia (heart rate <60 bpm) or asystole persists despite 30 seconds of effective positive pressure ventilation, followed by 30 seconds of coordinated cardiac compressions and ventilation, then 0.1–0.3 mL/kg of 1:10,000 epinephrine solution should be given rapidly via the intravenous route followed by 0.5–1.0 mL of normal saline flush. The emphasis on intravenous delivery of epinephrine rather than the previously acceptable endotracheal route mandates that delivery room resuscitation providers be well

trained in rapid placement of umbilical venous catheters. The endotracheal route is not efficacious or reliable, but it is must be used due to persistent lack of intravenous access, a higher dose (0.5–1.0 mL/kg) of epinephrine should be used, in hopes of improving efficacy. The higher endotracheal dose should always be drawn up in a larger 3- to 5-mL. Syringe to help alert the resuscitation team of the route for which the dose is intended, because high doses of epinephrine should not be given intravenously.

**Volume infusion:** Volume infusion should be given only if there is a high suspicion for rounding the delivery (cord avulsion, velamentous insertion of the cord, traumatic abruption, etc.); or if the baby appears to be in shock and unresponsive to apparently adequate resuscitation. If there is a suspicion of significant blood loss, then the best replacement fluid is emergency supply O-negative blood, but normal saline is acceptable until blood is available. It should be given in 10 mL/kg aliquots slowly over 5–10 minutes with assessment for response. It is important to remember, though, that the majority of severely depressed infants have suffered an asphyxial injury and are not hypovolemic. In an asphyxia-induced hypotension and bradycardia model (without hypovolemia), volume infusion during resuscitation increased pulmonary edema, decreased pulmonary dynamic compliance, and did not improve blood pressure either during or after the resuscitation. Thus, volume infusions during delivery room resuscitation may be detrimental and exacerbate poor cardiac output when hypovolemia is not present.

**Sodium bicarbonate:** There is no evidence to support use of sodium bicarbonate during resuscitation of the newborn. Its use in the newborn should be moved to postresuscitation care that can be guided by assessment of acid-base balance. Bicarbonate should never be given unless the lungs are being adequately ventilated. Otherwise, acidemia will be increased due to increased respiratory acidosis.

**Glucose:** Hypoglycemia causes derangement in myocardium. If baby is hypoglycemic and venous access is not available then intramuscular injection is given.

**Albumin:** This is the plasma expander. It helps to correct metabolic acidemia.

**Atropine:** It may be used for prolonged bradycardia, if it is vagal stimulated. In asphyxia it can be given intravenously or intratracheally.

### Postresuscitation Care

If 5-minute Apgar score is more than 7 and no other complication, baby is transferred to mother and kept under observation. If 5-minute Apgar score is less than 7 and baby has other complications like suspected meconium aspiration, and low birth weight (LBW), baby is transferred to NICU. Temperature of the infant is to be monitored to avoid hypothermia. Fluids are restricted to two-thirds of normal requirement to avoid syndrome of inappropriate antidiuretic hormone (SIADH) and to maintain fluid and electrolyte balance. Ventilator should be monitored depending upon blood gas reports. Metabolic complication should be monitored and treated. These include metabolic acidosis, hypoglycemia, hypocalcemia and hyperbilirubinemia.

Next step is to treat the complication such a convulsion by phenobarbitone 20 mg/kg and or phenytoin sodium 20 mg/kg loading dose and 3–4 mg/kg maintenance dose. Lumbar puncture is done to reduce intracranial tension in intraventricular hemorrhage. Infections are treated with appropriate antibodies.

### Subsequent Care

Most of them survive if they are breathing by 24 hours of age. Once the infant does not have

convulsions for 4–8 hours and does not show any neurological abnormality, anticonvulsion may be stopped. Long-term anticonvulsions should be given if the convulsions persist and if there are persisting electroencephalogram (EEG) changes associated with abnormal neurological signs.

*Prognosis is guarded if the following features persist:*

- Persisting fits and apnea attacks
- Prolonged hypotonia
- Prolonged hyperirritability
- Persistent vomiting
- Persistent failure to suck adequately

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# Neonatal Seizures

## PRESENTING COMPLAINTS

A 2-day-old girl was brought with the complaints of:

- Weak cry since 1 day
- Not taking feeds since 1 day
- Fever since 6 hours
- Uprolling of eyeballs since 20 minutes

## History of Presenting Complaints

A 2-day-old female newborn was referred to the pediatric outpatient department with the history of weak cry, not taking feeds regularly. Mother told the history of uprolling of the eyeballs. Mother felt that her daughter is warm. When mother brought these changes in her child to the notice of the ward sister, she referred to the pediatric outpatient department.

### CASE AT A GLANCE

#### Basic Findings

Length	: 49 cm (50th centile)
Weight	: 3 kg (25th centile)
Temperature	: 38.5°C
Pulse rate	: 140 per minute
Respiratory rate	: 28 per minute
Blood pressure	: 50/40 mm Hg

#### Positive Findings

##### History

- Weak cry
- Not taking feeds
- Uprolling of eyeballs
- Fever

##### Examination

- Febrile
- Depressed moro reflex
- Weak cry
- AF full

##### Investigation

- TLC: More
- CRP: Positive
- CSF: Turbid, leukocyte 102  
Glucose—10 mg/dL

## Past History of the Patient

The newborn baby was the second sibling of the nonconsanguineous marriage. Baby was born at term by normal vaginal delivery. There was no postnatal problem at the time of delivery. Baby cried immediately after the delivery. Cry of the baby was good. Child started breastfeeding immediately. Mother was having vaginal discharge for a long time for which she had treatment.

## EXAMINATION

Newborn baby was lying on the examination table. It was appearing to be appropriate for gestation. The child was lying without much movement. It was responding to the flickering of the sole by weak cry. Cry was very weak. Anterior fontanelle was full and tensed. Neonatal reflexes were sluggish.

The anthropometric measurements included the weight 3 kg (25th centile), the length 49 cm (50th centile), and head circumference 33 cm.

Baby was febrile (i.e., 38.5°C). The heart rate was 140 per minute and the respiratory rate was 28 per minute. The blood pressure recorded was 50/40 mm Hg.

There was hypotonia, depressed moro reflex and weak cry. Deep tendon reflexes are normal. Anterior fontanelle was full and bulging. Fundoscopic examination was normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 16,200 cells/cu mm
DC	: $P_{75} L_{20} M_2 E_3$
CRP	: Positive
RBS	: 38 mg/dL
Calcium	: 3.6 mg/dL
Sodium	: 132 mmol/L
Potassium	: 4.9 mmol/L
pH	: 7.37
PCO <sub>2</sub>	: 38 mm Hg
PO <sub>2</sub>	: 95 mm Hg
Chest X-ray	: NAD

CSF : Turbid  
 Leukocyte—102  
 60% polymorphs  
 Glucose—10 mg/dL  
 Protein—300 mg/dL  
 CSF Gram stain—negative

## DISCUSSION

Seizures are a common manifestation of serious central nervous system (CNS) disease in the newborn. Prompt diagnosis and intervention are indicated because seizures indicate serious underlying disease and may interfere with supportive care, e.g., ventilation and alimentation.

## PATHOPHYSIOLOGY

The immature brain has many differences from the mature brain that render it more excitable and more likely to develop seizures. In addition, the specific types of these receptors that are increased are those that are permeable to calcium (GluR2 AMPA receptors). This contributes to increased excitability and to the long-term consequences associated with seizures, particularly those resulting from perinatal hypoxia. Medications that block AMPA receptors, such as topiramate, may thus prove useful in this clinical setup.

Another difference is delay in the development of inhibitory GABAergic transmission. In fact, GABAergic in the immature brain has an excitatory function as the chloride gradient is reversed relative to the mature brain, with higher concentrations of chloride being present intracellularly than extracellularly. Thus, opening of the chloride channels in the immature brain results in depolarizing the cell and not in hyperpolarizing it. This phenomenon appears to be more prominent in male neonates, perhaps explaining their greater predisposition to seizures.

Although it is susceptible to developing seizures, the immature brain appears to be more resistant to the deleterious effects of seizures than the mature brain, as a result of increases in calcium binding proteins that buffer injury-related increases in calcium, increased extracellular space, decreased levels of the second messenger inositol triphosphate, and the immature brain's ability to tolerate hypoxic conditions by resorting to anaerobic energy metabolism.

## ETIOLOGY

When neonatal seizures occur, immediate attention must be directed toward the identification of

an underlying etiology in order to permit rapid and appropriate intervention (when available) as well as meaningful prediction of outcome. Although neonatal seizures may be due to numerous underlying causes, most result from a relatively few causes, e.g., hypoxic-ischemic cerebral injury, intracranial hemorrhage or metabolic derangements.

Seizures are distinctly uncommon manifestations of withdrawal from passive addiction to narcotics, e.g., heroin, methadone or barbiturates. In contrast, maternal cocaine abuse may be associated more commonly with epileptiform EEG abnormalities or seizures in newborns exposed in utero or by breastfeeding. This may relate to direct neuronal excitotoxicity, teratogenic effects, or destructive ischemic and hemorrhagic lesions.

Characteristically, severe, tonic seizures begin during the first hours of life, associated with apnea and severe hypoventilation, bradycardia, hypotonia, fixed and dilated pupils, and absence of extraocular movements in response to the doll's head maneuver. The later features are useful for distinguishing anesthetic intoxication from hypoxic-ischemic encephalopathy.

Early myoclonic encephalopathy presents within hours of birth with severe, fragmentary, refractory myoclonus, which often is worsened by handling or stimulation. Infants often have a high-arched palate. The initial neuroimaging is normal, but diffuse cerebral atrophy develops and affected infants frequently die in the first 2 years of life.

### A. Perinatal complications

These include neonatal encephalopathy, cerebral contusion and intracranial hemorrhage. This will account for 40% of seizures. Posthypoxic-ischemic state is suspected when there is abnormal fetal heart rate pattern, low Apgar score, jitteriness, lethargy, and seizures.

*Neonatal encephalopathy:* These children are apneic at birth, i.e., within 12 hours of life. The types of seizures may be subtle, tonic seizures and multifocal. This is associated with metabolic disorders such as hypocalcemia, hypoglycemia, inappropriate secretion of antidiuretic hormone (ADH), hyponatremia, and diabetes insipidus.

*Intracranial hemorrhage and CNS trauma:* The main cause is breech delivery and forceps delivery. Trauma may produce cerebral contusion or hemorrhage, subdural hematoma, subarachnoid bleeding. Seizures are seen on the 1st day of life. It is usually associated with prematurity and signs of encephalopathy.



**Primary subarachnoid hemorrhage:** This is mainly seen among premature babies. Seizures occur in 2nd day. Children will be normal in between the seizures. About 90% will have normal development.

**Periventricular hemorrhage:** This occurs within 3 days of life. These are mainly seen in premature children. Tonic seizures are presenting complaints. This is associated with rapid deterioration, respiratory arrest, and death.

**Subdural hemorrhage:** This results during the tearing of falx tentorium, superficial cortical veins. These are commonly seen with large babies and breech deliveries. Seizures occur on the 1st day. These are associated with cerebral contusion and hemorrhage.

## **B. Metabolic disorders**

- Hypoglycemia
- Hypocalcemia
- Hypomagnesemia
- Hyponatremia
- Hypernatremia
- Pyridoxine dependency
- Amino acid metabolism disorder
  - Maple syrup urine disorder
  - Phenylketonuria
  - Urea cycle disorder
- Organic acidemia
  - Methylmalonic acidemia
  - Propionic acidemia
  - Congenital lactic acidosis
- Biotin—response disorder
- Fructose intolerance

## **C. Infections**

- Bacterial
  - Meningitis
  - Brain abscess
- Viral
  - Coxsackievirus
  - Echovirus
  - Cytomegalovirus (CMV)
- Toxoplasmosis
- Syphilis

## **D. Developmental problems**

- Cerebral dysgenesis
- Neurocutaneous syndrome

## **E. Drugs**

- Narcotic and sedative withdrawal
- Inadvertent use of local anesthesia
- Theophylline

## **F. Polycythemia-hyperviscosity**

## **G. Focal infarcts**

## **H. Familial neonatal seizures**

### **I. Hypertensive encephalopathy**

Coarctation of aorta

### **J. Unknown cause**

Associated events causing CNS damage are increased cerebral blood flow, accompanying seizures may result in infarction of vascular bed. This is germinal matrix in preterm. Changes in the concentration of critical high energy phosphate bonds like ATP, phosphocreatine are the contributing factors. Depletion of the brain substrate such as cerebral glucose despite of increased cerebral blood flow and excessive release of synaptic excitatory amino acids such as glutamate, exert the toxic effect.

Incidence of etiology of newborn seizures is depicted in **Table 1**.

Causes of seizures can be classified depending on the day of appearance of seizures. These are placed as follows:

Day 1	<ul style="list-style-type: none"> <li>• Birth asphyxia</li> <li>• Birth injury</li> <li>• Hypoglycemia</li> <li>• Hypoglycemia hemorrhage</li> <li>• Congenital infection</li> </ul>
Day 2	<ul style="list-style-type: none"> <li>• Intracerebral bleed</li> <li>• Hypoxia</li> <li>• Hypoglycemia</li> </ul>
Day 3	<ul style="list-style-type: none"> <li>• Hypocalcemia</li> <li>• Inborn errors</li> </ul>
Day 4	<ul style="list-style-type: none"> <li>• Hypocalcemia</li> <li>• Drug withdrawal</li> <li>• Meningitis</li> </ul>

## **Hypoxic-ischemic Encephalopathy**

This is the most common cause of neonatal seizures, accounting 50–60% of patients. Seizures secondary to this encephalopathy occur within 12 hours of birth.

## **Vascular Events**

These include intracranial bleeds and ischemic strokes and account for 10–20% of patients. Three types of hemorrhage can be distinguished:

<b>TABLE 1:</b> Incidence of etiology.	
Perinatal hypoxia	50%
Infection	12%
Hypoglycemia	12%
Hypocalcemia	12%

primary subarachnoid hemorrhage, germinal matrix-intraventricular hemorrhage, and subdural hemorrhage. Patients with arterial strokes or venous sinus thrombosis can present with seizure and these can be diagnosed by neuroimaging. Venous sinus thrombosis could be missed unless MR or CT venography studies are requested.

### Intracranial Infections

Bacterial and nonbacterial infections account for 5–10% of the cases of neonatal seizures and include bacterial meningitis, TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus) infections, particularly herpes simplex encephalitis.

Hypoglycemia can cause neurologic disturbances and is very common in small neonants and neonates whose mothers are diabetic or prediabetic. The duration of hypoglycemia is very critical in determining the incidence of neurologic symptoms.

Hypoglycemia occurs at two peaks. The first peak corresponds to low birth weight infants and is evident in the first 2–3 days of life. The second peak occurs later in neonatal life and often involves large, full-term babies who consume milk that has an unfavorable ratio of phosphorus to calcium and phosphorus to magnesium. Hypomagnesemia is often associated with hypocalcemia. Hyponatremia can cause seizures and is often secondary to inappropriate antidiuretic hormone secretion.

Local anesthetic intoxication seizures can result from neonatal intoxication with local anesthetics administered into the infant's scalp.

Neonatal seizures can also result from disturbances in amino acid or organic acid metabolism. These are usually associated with acidosis and/or hyperammonemia. However, even in the absence of these findings, if a cause of the seizures is not immediately evident, then ruling out metabolic causes requires a full metabolic workup.

Pyridoxine and pyridoxal dependency disorders can cause severe seizures. These seizures, which are often multifocal clonic, usually start during the first few hours of life.

### Drug Withdrawal

Seizures can rarely be caused by the neonate's passive addiction and then drug withdrawal. Such drugs include narcotic analgesics, sedative-hypnotics, and others. The associated seizures appear during the first 3 days of life.

## Neonatal Seizure Syndromes

Seizure syndromes include benign idiopathic neonatal seizures (5th day fits), which are usually apneic and focal motor seizures that start around the 5th day of life. Patients have a good response to medications and a good prognosis. Autosomal dominant benign familial neonatal seizures have onset at 2–4 days of age and usually remit at 2–15 weeks of age. The seizures consist of ocular deviation, tonic posturing, clonic jerks, and, at times, motor automatisms. Interictal EEG is usually normal.

### CLINICAL FEATURES (FIG. 1)

Neonatal seizures differ considerably from seizures observed in older children, principally because the immature brain is less capable of propagating generalized or organized electrical discharges. The principal types of neonatal seizures are summarized below. Focal clonic seizures may be associated with focal cerebral infarction or traumatic cerebral contusion.

Benign neonatal sleep myoclonus occurs during active sleep in healthy premature and term newborns. Myoclonus may be florid and consists of either bilateral synchronous or asynchronous or asymmetric movements that are not stimulus sensitive, but which cease on arousal from sleep.

#### GENERAL FEATURES

- Convulsions
- Fever
- Not taking feeds
- Flabby

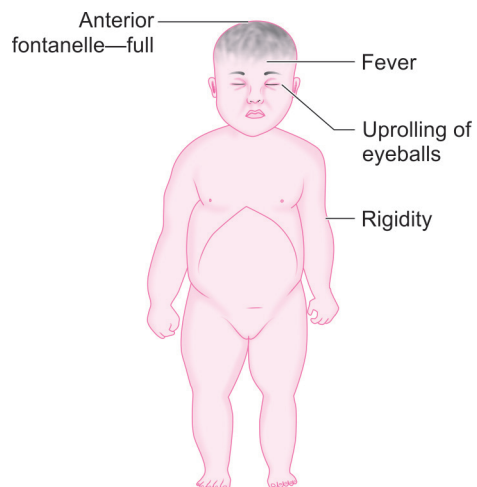


Fig. 1: Clinical features.

Infants with severe dysfunction of the CNS may have stimulus sensitive myoclonus, which may be associated with spike or sharp wave discharges on the EEG.

Subtle clinical phenomena correlate more frequently with simultaneous abnormal EEG discharges in premature than in term newborns.

The brain of the newborn is immature. Therefore, well-organized tonic-clonic type of convulsion is not seen in newborn. Hence, convulsions in newborn will have different presentations.

## Presentations of Convulsions

- Jerking of eyes
- Repetitive blinking or fluttering of eyelids
- Oral or buccal movements—drooling, sucking, yawning
- Tonic postures of limb
- Apnea

These are associated with hypocalcemia, hypoglycemia, neonatal encephalopathy and drug withdrawal. These are seen in premature children. It is also seen in child of diabetic mother with normal blood sugar and calcium levels.

## TYPES OF NEONATAL SEIZURES

The five main types of neonatal seizure are: subtle, clonic, tonic, spasms, and myoclonic seizures. Spasms, focal clonic, focal tonic, and generalized myoclonic seizures are, as a rule, associated with electrographic discharges (epileptic seizures), whereas motor automatisms, the subtle, generalized tonic and multifocal myoclonic episodes are frequently not associated with discharges and thus are thought to often represent release phenomena with abnormal movements secondary to brain injury rather than true epileptic seizures. To determine clinically whether such manifestations are seizures or release phenomena is often difficult, but precipitation of such manifestations by stimulation and aborting them by restraint or manipulation would suggest that they are not seizures.

Thus in many cases, specifically in sick neonates with history of neurologic insults, continuous bedside EEG monitoring helps make this distinction. Such monitoring has become the standard of care in most intensive care nurseries.

## Subtle Seizures

This accounts for 50% of convulsions in newborn. It may be subcortical in origin. This may not be associated with epileptic form or hypersynchronous EEG. Subtle seizures include transient eye deviations, nystagmus, blinking, mouthing,

abnormal extremity movements (rowing, swimming, bicycling, pedaling, and stepping), fluctuations in heart rate, hypertension episodes, and apnea. Subtle seizures occur more commonly in premature than in full-term infants.

## Clonic Seizures

Here movements are localized, clonic jerking type. There will not be loss of consciousness. Clonic seizures can be focal or multifocal. Multifocal clonic seizures incorporate several body parts and are migratory in nature. The migration follows a non-Jacksonian trend; e.g., jerking of the left arm can be associated with jerking of the right leg. Generalized clonic seizures that are bilateral, symmetric, and synchronous are uncommon in the neonatal period presumably due to decreased connectivity associated with incomplete myelination at this age. This is associated or precipitated by metabolic disturbances and trauma. Trauma may be cerebral contusion, subarachnoid hemorrhage or focal infarct. Unifocal abnormal EEG is reported. Prognosis is good.

## Tonic Seizures

Movements may be focal or localized type. These may resemble decerebrate or decorticate rigidity. These are associated with eye movements or apnea. This is more often seen with premature child. Focal tonic seizures include persistent posturing of a limb or posturing of trunk or neck in an asymmetric way often with persistent horizontal eye deviation. Generalized tonic seizures are bilateral tonic limb extension or tonic flexion of upper extremities often associated with tonic extension of lower extremities. This is associated with CNS disease, intraventricular hemorrhage, multifocal, abnormal EEG with burst suppression pattern, with extremely attenuated amplitude. Prognosis is poor.

## Spasms Seizures

Spasms are sudden generalized jerks lasting 1–2 seconds that are distinguished from generalized tonic spells by their shorter duration and by the fact that spasms are usually associated with a single, very brief, generalized discharge.

## Myoclonic Seizures

Myoclonic seizures are divided into focal, multifocal, and generalized types. Myoclonic seizures can be distinguished from clonic seizures by the rapidity of the jerks (<50/sec) and by their lack

of rhythmicity. Focal myoclonic seizures characteristically affect the flexor muscles of the upper extremities and are sometimes associated with seizure activity on EEG.

Movements are single or multiple with slow jerks. Movements are synchronous. This involves upper and lower limbs with CNS pathology. Burst suppression pattern EEG with focal sharp transient waves is seen. These will evolve into hypsarrhythmias. Prognosis is poor.

## SEIZURES VERSUS JITTERINESS

Jitteriness can be defined as rapid motor activities, such as a tremor or shake, that can be ended by flexion or holding the limb. Seizures, on the other hand, generally do not end with tactile or motor suppression. Jitteriness, unlike most seizures, is usually induced by a stimulus.

### Jitteriness and Clonus

These are characterized by absence of abnormal gaze or eye movements. These can be provoked by stimulation or by stretching of the joint. Passive flexion or gentle restrain can stop the movements. These are accompanied by increased blood pressure or bradycardia. There is no associated EEG abnormality. Tremors are the prominent type of movements.

- Jitteriness is not accompanied by abnormal eye movements.
- Jitteriness may be spontaneous or stimulus sensitive.
- The flexion and extension phases of the tremor are equal in amplitude compared to the unequal phases observed with clonic seizure movements.
- Jitteriness may be stopped by passive flexion or repositioning of the affected body part.

### Causes of Jitteriness

- Normal infants
- Hypocalcemia
- Cerebral hyperexcitability
- Infants of diabetic mother
- Hypoglycemia
- Congenital thyrotoxicosis
- Drug toxicity
  - Atropine
  - Ephedrine

## DIAGNOSIS

Some cases can be correctly diagnosed by simply taking the prenatal and postnatal history, and

performing an adequate physical examination. Depending on the case, additional tests or procedures can be performed. EEG is considered the main tool for diagnosis. It can show paroxysmal activity (e.g., sharp waves) in between the seizures and electrographic seizure activity if a seizure is captured. However, some neonatal seizures might not be associated with EEG abnormalities.

### ESSENTIAL DIAGNOSTIC POINTS

- Varying clinical presentation
- Results from underlying CNS dysfunction or can cause CNS damage
- Intravenous anticonvulsants in correct doses are essential
- Abnormal eye movements, limb movements, oral-buccal-lingual movements, and apnea may be the presentation
- Treatment of underlying cause

Continuously monitoring the EEG at the bedside in the neonatal intensive care unit (NICU) for neonates at risk for neonatal seizures and brain injury is part of routine clinical practice in most centers, providing real-time measurements of the brain's electrical activity and identifying seizure activity.

Careful neurologic examination of the infant might uncover the cause of the seizure disorder. Examination of the retina might show the presence of chorioretinitis, suggesting a congenital TORCH infection in which case titers of mother and infant are indicated. Inspection of the skin might show hypopigmented lesions characteristic of tuberous sclerosis (seen best on UV light examination) or the typical crusted vesicular lesions of incontinentia pigmenti; both neurocutaneous syndromes are often associated with generalized myoclonic seizures beginning early in life. An unusual body or urine odor suggests an inborn error of metabolism.

Blood should be obtained for determinations of glucose, calcium, magnesium, electrolytes, and blood urea nitrogen. If hypoglycemia is a possibility, serum glucose testing is indicated so that treatment can be initiated immediately. Hypocalcemia can occur in isolation or in association with hypomagnesemia. A lowered serum calcium level is often associated with birth trauma or a CNS insult in the perinatal period.

A lumbar puncture is indicated in virtually all neonates with seizures, unless the cause is obviously related to a metabolic disorder such as hypoglycemia or hypocalcemia. The CSF findings can indicate a bacterial meningitis or aseptic encephalitis. Prompt diagnosis and appropriate therapy

improve the outcome for these infants. Bloody CSF indicates a traumatic tap or a subarachnoid or intraventricular bleed. Immediate centrifugation of the specimen can assist in differentiating the two disorders. A clear supernatant suggests a traumatic tap, and a xanthochromic color suggests a subarachnoid bleed. Mildly jaundiced normal infants may have a yellowish discoloration of the CSF that makes inspection of the supernatant less reliable in the newborn period.

Additional causes include maternal diabetes, prematurity, DiGeorge syndrome, and high-phosphate feedings. Hypomagnesemia ( $<1.5$  mg/dL) is often associated with hypocalcemia and occurs particularly in infants of malnourished mothers. In this situation, the seizures are resistant to calcium therapy but respond to intramuscular magnesium,  $0.2$  mL/kg of a 50% solution of  $\text{MgSO}_4$ . Serum electrolyte measurement can indicate significant hyponatremia (serum sodium  $<115$  mEq/L) or hypernatremia (serum sodium  $>160$  mEq/L) as a cause of the seizure disorder.

Many inborn errors of metabolism cause generalized convulsions in the newborn period. Because these conditions are often inherited in an autosomal recessive or X-linked recessive fashion, it is imperative that a careful family history be obtained to determine if there is a consanguinity, or whether siblings or close relatives developed seizures or died at an early age. Serum ammonia determination is useful for screening for the hypoglycemic hyperammonemia syndrome and for suspected urea cycle abnormalities.

Maple syrup urine disease (MSUD) should be suspected when a metabolic acidosis occurs in association with generalized clonic seizures, vomiting, bulging fontanelle, and muscle rigidity during the 1st week of life. The result of a rapid screening test using 2,4-dinitrophenylhydrazine that identifies ketoderivatives in the urine is positive in MSUD.

Pyridoxine dependency must be considered when seizures begin shortly after birth with signs of fetal distress in utero and are resistant to conventional anticonvulsants such as phenobarbital or phenytoin. The history may suggest that similar seizures occurred in utero. When pyridoxine-dependent seizures are suspected, 100–200 mg of pyridoxine or pyridoxal phosphate should be administered intravenously during the EEG, which should be promptly performed once the diagnosis is considered. The seizures abruptly cease, and the EEG often normalizes in the next few hours or longer.

## INVESTIGATIONS

Investigations of neonatal convulsions can be categorized as:

- **Immediate:** These are done at the time of convulsions, as the investigations done will help in the immediate management.
  - Blood glucose
  - Serum electrolytes—sodium, potassium
  - Serum calcium
  - PCV
  - Acid-base gas analysis
- **Early:** This is done once the baby has stopped convulsing. This will help to find out the cause.
  - CBC
  - Blood culture
  - Lumbar puncture
  - CT scan
- **Late:** These are not always necessary. This is indicated when the convulsions are recurrent. Etiology has not been established by routine investigations.
  - Serum magnesium
  - Amino acid chromatography
  - Urine for drug screening
  - CT scan
  - MRI
  - EEG

### LABORATORY SALIENT FINDINGS

- Blood sugar
- Serum electrolytes, calcium, magnesium
- Hematocrit
- Lumbar puncture
- CT scan
- EEG
- Septic profile
- Screening for inborn error of metabolism

## TREATMENT

The mainstay in the therapy of neonatal seizures is the diagnosis and treatment of the underlying etiology (e.g., hypoglycemia, hypocalcemia, meningitis, drug withdrawal, trauma), whenever one can be identified.

### Lorazepam

The initial drug used to control acute seizures is usually lorazepam. Lorazepam is distributed to the brain very quickly and exerts its anticonvulsant effect in  $<5$  minutes. It is not very lipophilic and does not clear out from the brain very rapidly. Its action can last 6–24 hours. Usually it does not cause hypotension or respiratory depression. The dose is  $0.05$  mg/kg (range:  $0.02$ – $0.10$  mg/kg)



every 4–8 hours intravenously. It is useful in acute situation. This is given for about 2–5 minutes.

### Diazepam

Diazepam can be used as an alternative initial drug. It is highly lipophilic, so it distributes very rapidly into the brain and then is cleared very quickly out, carrying the risk of recurrence of seizures. Like other IV benzodiazepines, it carries a risk of apnea and hypotension, particularly if the patient is also on a barbiturate, so patients need to be observed for 3–8 hours after administration. The usual dose is 0.1–0.3 mg/kg IV over 3–5 minutes, given every 15–30 minutes to a maximum total dose of 2 mg. However, because of the respiratory and blood pressure limitations and because the IV preparation contains sodium benzoate and benzoic acid, it is currently not recommended as a first-line agent. The initial dose is 0.1–0.3 mg/kg. This acts synergistically with phenobarbitone, hence there is a high risk of respiratory arrest.

### Midazolam

Midazolam can be used as an initial drug as a bolus or as a second- or third-line drug as a continuous drip for patients who did not respond to phenobarbital and/or to phenytoin. The doses used have been in the range of 0.05–0.1 mg/kg IV initial bolus, with a continuous infusion of 0.5–1 µg/kg/min IV that can then be gradually titrated upward, if tolerated, every 5 minutes or longer, to a maximum of approximately 33 µg/kg/min (2 mg/kg/h).

### Phenobarbital

Phenobarbital is given in the dose of 10–20 mg/kg to control seizures for several minutes. If the seizure persists, even after 1 hour, a second dose of 10 mg/kg can be repeated. If the seizure still persists, another dose of 10 mg/kg can be repeated after 2–4 hours. The maximum loading dose is 30–40 mg/kg. Cumulating loading dose greater than 20 mg/kg requires careful monitoring of blood pressure and respiratory status. Apnea and hypertension are rarely encountered. Respiratory support may be needed after phenobarbital loading. Twenty-four hours after starting the loading dose, maintenance dosing can be started at 3–6 mg/kg/day usually administered in two separate doses.

In seizure free period, phenobarbitone is given at the dose of 15–20 mg/kg IV. This will help to attain the therapeutic plasma levels. The maintenance dose of phenobarbitone is 3.5–4.5 mg/kg/day.

This can be given as a single dose or divided into two doses.

Therapeutic plasma level range is from 15 to 45 mg/dL. This should be measured at least 1 hour after IV dose or 2–4 hours oral dose. The lowest therapeutic dose is 15–30 mg/dL.

### Phenytoin and Fosphenytoin

The dose of 15–25 mg/kg IV in normal saline at a rate not faster than 1 mg/kg/min is given. The rate at which the dose should be given must not exceed 0.5–1 mg/kg/min in order to prevent cardiac problems, and the medication needs to be avoided in patients with significant heart disease. Heart rate should be monitored while administering the drug. A maintenance dose is 4–8 mg/kg/day. This is divided into two to three doses. Therapeutic plasma level is 10–20 mg/dL.

Fosphenytoin, which is a phosphate ester prodrug, is preferable. It is highly soluble in water and can be administered very safely intravenously and intramuscularly, without causing injury to tissues. Fosphenytoin is administered in phenytoin equivalents (PE). The usual loading dose of fosphenytoin is 15–20 PE/kg administered over 30 minutes. Maintenance doses of 4–8 PE/kg/day can be given.

If required, as well as correction of hypoglycemia, hypocalcemia or other metabolic derangements. If seizures persist, a single loading dose of phenobarbitone (20 mg/kg) should be administered intravenously, which may be followed by additional doses of 5 mg/kg to a total of 40 mg/kg (including loading dose) as required, if there is no cardiac decompensation. If seizures are still uncontrolled, a single loading dose of phenytoin (20 mg/kg) may be administered slowly with concomitant careful monitoring of cardiac function. If seizures remain refractory to therapy, the use of benzodiazepine, lorazepam or midazolam is recommended.

Seizures in neonatal period are often life-threatening. It may lead to incredible brain damage. Vital parameters should be maintained. Serum electrolytes and pH should be monitored. Underlying cause should be treated. IV therapy and glucose therapy are included.

Serum glucose level should be maintained around 70–120 mg/dL, 2–4 mL/kg of 25% dextrose is given over 3–4 minutes. This should be followed by 4–8 mg/kg/min as maintenance dose.

*Pyridoxine dependency:* This is diagnosed by giving pyridoxine 50 mg IV as a therapeutic trial. The diagnosis is confirmed if seizure stops within

a minute. Maintenance dose of 10–100 mg of pyridoxine orally four times a day is advised. In case of deficiency the dose is 5 mg orally.

Duration of Therapy

Duration of therapy is related to the risk of developing later epilepsy in infants suffering from neonatal seizures, which ranges from 10–30% and depends on the individual neurologic examination, the etiology of the seizures, and the EEG at the time of discharge from the hospital. In general, if the EEG at the time of discharge does not show evidence of epileptiform activity, then medications are usually tapered at that time. If the EEG remains paroxysmal, then the decision is usually delayed for several months after discharge.

Other Anticonvulsants

Primidine, carbamazepine and valproic acid are used.

Treatment for Refractory Seizures

If the seizures are refractory, 40 mg/kg of initial dose of phenobarbitone, then phenytoin at the dose of 20 mg/kg is administered. Then if the seizures remain unresponsive, benzodiazepine (diazepam, lorazepam) or paraldehyde is used. Simultaneous EEG should be performed to document cessation of seizure activity. Magnesium sulphate at the dose of 0.2 mL/kg/dose of 50% solution can be used. Pyridoxine is also used at the dose of 50–100 mg IV.

If the convulsions are intractable and baby is in state convulsions, clonazepam 50 µg/kg IV slowly for 2–5 minutes is given. Alternatively clonazepam 100–200 µg/kg can be given intravenously over 30 seconds. Benzodiazepam can be repeated as and when needed. Midazolam can be repeated as and when needed. Midazolam 0.05–0.15 mg/kg/dose is effective when given intramuscularly.

Follow-up of Anticonvulsant Therapy

All the medications which are used to control the seizures can be stopped. The only maintenance dose of phenobarbitone is continued. Indications for stopping anticonvulsants are: normal examination findings, absence of recurrent, and non-epileptiform seizures.

The duration of the therapy is guided by neurological status of the infant, cause of the seizures and EEG findings. The infant is evaluated at 6–8 weeks. If there is no recurrence of seizures, CNS examination and EEG are normal, the phenobarbitone is stopped. When the phenobarbitone is continued, the child is evaluated at the age

of 6 months. The infant is treated like a case of epilepsy if the seizures are recurrent or if there are any evidence of neuronal disabilities or if these are EEG normalities at 6 months.

PROGNOSIS

The most important determinant of outcome is the underlying neurologic disease. In addition, the early onset of seizures, frequent or prolonged seizures and seizures that are refractory to multiple anticonvulsants often are associated with poor prognosis. However, in a significant proportion of newborns, the EEG is borderline, equivocal or contains less marked abnormalities that are associated with an uncertain prognosis.

Normal outcome	56%
Neurological sequelae	30%
Death	15%

Seizures are more common with the gestational age less than 30 weeks. Neonatal mortality is more with lesser gestational age. Seizures of different Etiology will have different prognosis. Outcome will reflect the seriousness of disease. Prognosis depends upon the type of the seizure. Only 10% of the seizure children will have normal EEG. About 90% of the seizure children will burst suppression pattern with electrical silence with marked voltage suppression. Fifty percent of seizures with immaturity and voltage asymmetry will have neurological deficits.

Bad Prognostic Factors

- Apgar score —less than 6 at 5 minutes
- 5 minutes intermittent positive pressure ventilation (IPPV) following birth
- Early onset of seizure
- Seizures lasting more than 30 minutes
- Hypotonia at 5 minutes following birth
- Uncontrolled seizures for 3 or more days
- Presence of tonic or myoclonic seizures

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# Neonatal Hypoglycemia

## PRESENTING COMPLAINTS

A newborn baby was brought with the complaints of:

- Not active since 4 hours
- Apathy since 4 hours
- Not taking feeds since 2 hours

## History of Presenting Complaints

The newborn baby was brought to the pediatric outpatient department with history of apathy, not active since 4 hours and not taking feeds since 2 hours. The child was delivered about 12 hours back in the hospital. This was normal full-term delivery. Newborn was delivered by vertex presentation. Baby cried immediately after the delivery. Cry of the baby was good. The Apgar score was 8 and 10 at 1 and 5 minutes respectively. Mother was advised to feed her baby after sometime. Mother told that his son was sucking at her breast in the beginning. But now he was not at all getting up even after the tactile stimulus. That worried her and came to show her son to the pediatrician.

Antenatal history and check-up showed development of diabetes in the mother after

1st trimester. She was advised glucose tolerance test (GTT) and diagnosed to have gestational diabetes. But her diabetes status was under control with medicines. All the antenatal scanning to rule out congenital anomalies were normal.

## EXAMINATION

The newborn was big in size. The newborn baby was lying on the examination table, without any movements. Child was not active. Hypotonia was present. His cry was feeble after tactile stimulation. Neonatal reflexes were not satisfactory. The anthropometric measurements included, weight was 4 kg (97th centile), length was 53 cm (97th centile), and head circumference of 35 cm. Child was afebrile, heart rate was 146 per minute, respiratory rate was 24 per minute. The blood pressure recorded was 50/40 mm Hg. All systemic examinations were normal. There was no clinical evidence of congenital anomalies.

## INVESTIGATIONS

Hemoglobin	: 14 g/dL
TLC	: 12,400 cells/cu mm
DC	: $P_{68} L_{28} E_2 M_2$
RBS	: 40 mg/dL
Blood urea	: 20 mg/dL
Creatinine	: 1 mg/dL
Serum calcium	: 8 mg/dL
CRP	: Negative
Blood culture and sensitivity	: Sterile
Chest X-ray	: NAD
ECHO	: NAD

## DISCUSSION

Hypoglycemia is the metabolic disorder, where blood glucose level is less than 45 mg/dL. During the gestation, the glucose is freely transferred across the placenta by process of facilitated diffusion. After the birth, infant must adjust with sudden withdrawal of transplacental supply. There will

### CASE AT A GLANCE

#### Basic Findings

Length	: 53 cm (97th centile)
Weight	: 4 kg (97th centile)
Temperature	: 37°C
Pulse rate	: 146 per minute
Respiratory rate	: 24 per minute
Blood pressure	: 50/40 mm Hg

#### Positive Findings

##### History

- Diabetic mother
- Not active
- Not taking feeds

##### Examination

- Big baby
- Neonatal reflexes: Not satisfactory

##### Investigation

- Random blood sugar (RBS): 40 mg/day

be decrease in blood sugar level between 1 and 3 hours of life. This fall is accentuated in preterm infant, infants of diabetic mother, birth asphyxia, and in intrauterine growth restriction (IUGR) babies.

It is a metabolic disorder, where the blood glucose level is less than 45 mg/dL. Any child with blood glucose less than 40 mg/dL should be evaluated. Incidence is 0.4%.

During the gestation, glucose is freely transferred across the placenta by the process of facilitated diffusion. However, after the birth, infant must adjust with sudden withdrawal of this transplacental supply. In all infants, there is nadir in blood sugar between 1 and 3 hours of life. This fall is accentuated in preterm infants, infants of diabetic mother, infants with erythroblastosis fetalis, asphyxiated infants and in small for gestational age (SGA) infants. Brain dysfunction occurs at 45 mg/dL at any age or gestation.

Because plasma or blood glucose concentrations only roughly reflect glucose turnover, a plasma glucose concentration less than 40 mg/dL should be used to define hypoglycemia.

All conditions associated with the development of hypoglycemia in the neonate result from one or a combination of two basic mechanisms: inadequate production or excessive tissue use. Inadequate glucose production results from a lack of glycogen stores, an inability to synthesize glucose or both. Excessive tissue use results from increased insulin secretion.

## CLINICAL FEATURES (FIG. 1)

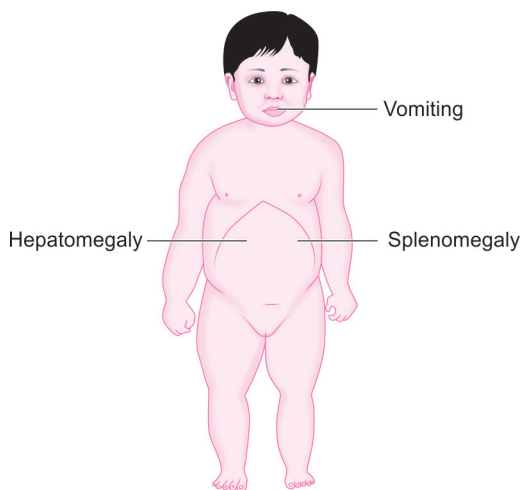
The clinical features of hypoglycemia are many. These are listed here:

- Lethargy, apathy, weak or high pitched cry, poor feeding
- Tremors, jitteriness, apnea and cyanosis
- Seizures
- Vomiting
- Macrosomia favors hyperinsulinism
- Jaundice—galactosemia, sepsis
- Hepatomegaly—glycogen storage disorder
- Splenomegaly—Rh immunization

## CAUSES

Causes of hypoglycemia:

- Infants of diabetic mother
- Erythroblastosis fetalis
- Prematurity
- IUGR
- Birth asphyxia



**Fig. 1:** Clinical features.

- Hypothermia
- Galactosemia
- Adrenal insufficiency
- Congenital hypopituitarism
- Polycythemia

The third trimester of pregnancy is an important period for hepatic glycogen deposition. An infant delivered prematurely without having had the benefit of part of or the entire third trimester will have limited hepatic glycogen stores. The greater the degree of prematurity, the less glycogen will be present. Small for gestational age premature infants are at extremely high risk for development of hypoglycemia because available nutrients in life are channeled toward growth, with little set aside for glycogen storage. For this reason, SGA premature infants have extremely limited glycogen stores.

Hypoxia, acidosis and alterations in fetal blood pressure and flow can stimulate catecholamine secretion in utero, which in turn will mobilize hepatic glycogen stores. In addition, hypoxia increases the rate of anaerobic glycolysis, thereby accelerating glucose use. These events deplete fetal glycogen stores and place the infant at risk for hypoglycemia after delivery.

Full term and premature SGA neonates are at great risk for development of hypoglycemia as a result of inadequate hepatic glycogen stores. A delay in the induction of gluconeogenic capability probably is responsible for this prolonged hypoglycemia. These SGA neonates have elevated plasma concentrations of gluconeogenic precursors, suggesting an inability to convert exogenous gluconeogenic precursors such as alanine to glucose.

Infants of diabetic mothers are at great risk for development of hypoglycemia as a result of the carry-over of the fetal hyperinsulinemic state into neonatal life. They have elevated plasma insulin concentrations and release insulin briskly in response to glucose challenge. The problems of the infant of diabetic mother (IDM) are presented in the following sections.

Infants with Beckwith-Wiedemann syndrome, erythroblastosis fetalis and those whose mothers have taken chlorpropamide or benzthiazides are at risk for development of hypoglycemia as a result of hyperinsulinism. Infants with erythroblastosis fetalis caused by Rh compatibility were reported in the past to be at risk for hypoglycemia from hyperinsulinism secondary to  $\beta$ -cell hyperplasia.

Maternal use of chlorpropamide and benzthiazide can directly increase insulin secretion in the neonate.  $\beta$ -sympathomimetic agents used to stop premature labor have been reported to cause neonatal hypoglycemia. These drugs stimulate glycogen breakdown and gluconeogenesis in the mother and fetus. Large for gestational age (LGA) infants whose mothers do not have diabetes mellitus are at risk for transient hypoglycemia. This is particularly true for LGA infants of obese women. Sepsis in a neonate often is heralded by hypoglycemia or hyperglycemia. Hypoglycemia is a well acknowledged complication of the neonatal polycythemia-hyperviscosity syndrome.

Although polycythemia is more likely to occur in SGA and LGA infants who are at risk for hypoglycemia for other reasons, hypoglycemia occurs at an increased rate in polycythemic approximately grown infants. Infants who have suffered hypothermia are at increased risk for development of hypoglycemia. This may result from increased availability of catecholamines, which would deplete glycogen reserves. Tissue use of glucose also might be increased under these conditions.

#### GENERAL FEATURES

- Lethargy, apathy, weak or high pitched cry
- Poor feeding
- Seizures
- Jaundice

#### DIFFERENTIAL DIAGNOSIS

- Adrenal insufficiency
- Renal failure
- Central nervous system (CNS) disease
- Asphyxia
- Liver failure
- Cardiac failure
- Sepsis

#### DIAGNOSIS AND TREATMENT

High babies should receive adequate breast-feeding and should be assessed. Small babies not able to suck effectively on the breast should receive expressed breast milk by alternate methods.

If the blood sugar level is more than 20 mg/dL in asymptomatic baby, a trail of oral feeds is given and blood sugar is tested after 30–45 minutes. If the sugar values above 40 mg/dL, frequent feeding is advised and blood sugar level is monitored every 6 hourly for 48 hours. If blood sugar level persists below 40 mg/dL, baby should receive IV glucose infusion. If the initial blood sugar level is less than 20 mg/dL, IV glucose infusion is started.

In infants with the risk of hypoglycemia, blood glucose level should be checked at 3, 6, 12 and 24 hours of age. These children should be given 10% glucose and water every 2–4 hourly, until the glucose level is stable. The blood glucose should be maintained above 2.0 mmol/dL.

In symptomatic hypoglycemia, blood glucose level should be monitored every 1–4th hourly. Milk feeds are better than glucose feeds.

#### ESSENTIAL DIAGNOSTIC POINTS

- Blood sugar less than 40 mg/dL in term and preterm infants
- Often asymptomatic detected on screening
- Manifestations; lethargy, poor cry, poor activity, refusal of feeds, apnea, cyanosis, tremors, and rarely seizures
- Should be treated quickly and promptly as it produces brain damage

Glucose in the dose of 2–4 mL/kg (0.5–1.0 mg/kg) of 25% dextrose are given by rapid intravenous infusion. The rate of administration should be 1 mL per minute. This should be followed by continuous infusion of glucose in the dose of 4–8 mg/kg/min.

Some infants with hyperinsulinism and infants with IUGR will require glucose dose 12–15 mg/kg/min. Glucose is tapered to 4–6 mg/kg/min after monitoring the glucose level. Glucagon 0.1 mg/kg intramuscularly is given with the maximum dose of 1 mg/kg in infants with good glycogen storage.

Small for the date babies should be started with milk feeds within 2 hours of the birth and can be fed every 3rd hourly for the first 24 hours. Premature babies should have an intravenous line started immediately. About 10% glucose infusion is started with maintenance sodium.

If hypoglycemia is found in child born to diabetic mother, feeding should be started as early as possible. Feeding should be given 3rd hourly for



the first 24 hours. Breastfed babies should be put to the breast. They may require complimentary milk formula if the glucose level falls below 1.5 mmol/L.

#### LABORATORY SALIENT FINDINGS

- Hematocrit
- Sepsis screen
- Blood grouping for Rh incompatibility
- Investigate maternal diabetes

In comatose children or in babies with convulsions, 25% dextrose intravenously for 1 mL/min and 10% glucose infusion at the rate of 60–90 mL/kg/day is given. Then it should be tapered to avoid rebound phenomenon. This is seen especially with hyperinsulinemia.

If the glucose level remains low, then 15–20% dextrose infusion is started. Then hydrocortisone is started in the dose of 2.5 mg/kg 12th hourly. If the blood glucose level is still less than 46 mg/dL, then glucagon in the dose of 0.1 mg/kg is used. This should be given intramuscularly.

### Treatment of Refractory Hypoglycemia

**Corticosteroids:** This reduces peripheral glucose utilization and promoted gluconeogenesis. Hydrocortisone is given in the dose of 5 mg/kg.

**Glucagon:** This releases glycogen from hepatic stores and promotes gluconeogenesis. The dose of glucagon is 0.25 mg/kg.

**Epinephrine:** This promotes gluconeogenesis and glycogenolysis and augments glycogen secretion. It inhibits insulin secretion.

**Diazoxide therapy:** This is used only in extreme cases after other therapies have failed.

All infants at risk for development of hypoglycemia should undergo frequent plasma glucose determinations. Infants at risk for hypoglycemia should be checked frequently during the first 4 hours of life and then at 4-hour intervals until the risk period has passed. If an infant is feeding, blood sampling should be done before feeding. For IDMs and SGA infants, the screening should continue for at least 24 hours.

Intravenous administration of glucose in a quantity sufficient to meet tissue requirements is the treatment of choice for hypoglycemia. The administration of 10 or 15% dextrose solution at 5–10 mL/kg body weight, followed by a continuous infusion at 5–6 mg/kg body weight per minute of glucose, will increase plasma glucose concentrations to 40 mg/dL or greater and acutely meet tissue requirements. The maintenance rates may require adjustment depending on the etiology of hypoglycemia.

Glucagon and epinephrine increase glucose production. Because both mobilize hepatic glycogen stores, their efficacy in treating hypoglycemia is variable, particularly in infants with limited hepatic stores. The numerous cardiovascular effects of epinephrine also limit its usefulness in infants.

Infants who are hypoglycemia for prolonged periods as a result of an inability to produce glucose can be treated with corticosteroids (hydrocortisone 5 mg/kg/day every 12 hours; prednisone 2 mg/kg/day orally). Steroids exert some of their effects by inducing gluconeogenic enzyme activity.

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# Neonatal Pathological Jaundice

## PRESENTING COMPLAINTS

A 2-day-old newborn was brought with the complaints of:

- Yellowish discoloration of skin since 2 days
- Not taking feeds since 1 day

## History of Presenting Complaints

A 2-day-old newborn baby was brought to pediatric outpatient department with history of yellowish discoloration of skin. Mother told that she had noticed yellowish discoloration 5–6 hours after the delivery. She also revealed that her baby was not taking feeds or sucking at breasts since morning, i.e., on 2nd day. She brought this to the notice of the resident working in ward. Later boy was referred to pediatric outpatient department for further management.

## Past History of the Patient

This newborn boy was the second sibling of non-consanguineous marriage. Baby was born at term by normal vaginal delivery. There was no postnatal problem at the time of delivery. Baby cried

immediately after the delivery. Cry of the baby was good. Child started breastfeeding immediately. Mother was not having any antenatal health records. On leading question, there was one abortion before the delivery of the present baby. The first child was the girl baby, and she never had any problem at the time of delivery.

## EXAMINATION

Child was lying on the examination table. It was appearing to be appropriate for gestation. The child was lying without much movement. It was responding to the flickering of the sole by crying. But the cry was very weak. Anterior fontanelle was depressed. Neonatal reflexes were sluggish.

The anthropometric measurements included, weight was 3 kg (25th centile) and length was 49 cm (50th centile). The head circumference was 33 cm.

Baby was afebrile, the heart rate was 140 per minute and respiratory rate was 28 per minute, blood pressure recorded was 50/40 mm Hg.

Baby was pale. Icterus was present even on the palm and sole. There was no edema, no lymphadenopathy. All the systemic examinations were normal.

### CASE AT A GLANCE

#### Basic Findings

Length	: 49 cm (50th centile)
Weight	: 3 kg (25th centile)
Temperature	: 37°C
Pulse rate	: 140 per minute
Respiratory rate	: 28 per minute
Blood pressure	: 50/40 mm Hg

#### Positive Findings

##### History

- Yellowish discoloration
- Not taking feeds

##### Examination

- Hemoglobin: 8.8 g/dL
- Blood group of child: O positive
- Packed cell volume (PCV): 58%
- Raised serum bilirubin
- Increased reticulocyte count
- Coombs test: Positive

## INVESTIGATION

Hemoglobin	: 8.8 g/dL
TLC	: 12,300 cells/cu mm
DC	: $P_{72} L_{18} E_6 M_2 B_2$
Blood group of mother	: O negative
Blood group of the newborn	: O positive
PCV	: 58%
Peripheral blood smear	: Immature RBCs were present
Reticulocyte count	: 5%
Coombs test	: Positive
Serum bilirubin	: 28 mg/dL
	Direct 2 mg/dL
	Indirect 26 mg/dL

## DISCUSSION

### Introduction

Jaundice, a yellow discoloration of the skin and sclerae resulting from bilirubin deposition in tissues arises when the rate of bilirubin production exceeds the rate of its elimination. Although jaundice can result from an increase in either unconjugated (indirect) or conjugated (direct) bilirubin, a rise in the indirect fraction is the most common cause of newborn jaundice and is the focus of this chapter.

### Pathological Hyperbilirubinemia

Delayed physiologic processes or pathologic conditions can result in severe hyperbilirubinemia requiring treatment. Jaundice occurring in the first 24 hours of life or persisting beyond 2 weeks of age in a term infant, a rapid rate of rise of bilirubin  $>0.2$  mg/dL/h, a serum bilirubin level greater than the 95th percentile for age in hours, or a direct bilirubin level  $>1$  mg/dL are all suggestive of pathologic jaundice.

Pathologic jaundice is due to an imbalance between bilirubin production and elimination. Increased production can result from hemolysis arising from blood group incompatibilities, erythrocyte enzyme deficiencies, or structural defects of the erythrocytes. Increased bilirubin production is also seen in premature infants because of the shortened red cell lifespan; in infants of diabetic mothers due to polycythemia or ineffective erythropoiesis; in infants with dosed-space bleeding, such as bruising or hemorrhage into internal organs due to the breakdown of extruded blood; in infants with polycythemia; and in infants with sepsis. Decreased elimination of bilirubin can result from either a genetic defect in hepatic uptake, as seen in newborn infants with a polymorphic variant of the organic anion transporter protein (OATP-2) gene, or impaired conjugation of bilirubin from inherited defects in uridine 5'-diphospho-glucuronosyltransferase (UGT) as seen in Gilbert syndrome and Crigler-Najjar syndrome types I (severe deficiency) and II (less severe form). In Gilbert syndrome, the mildly decreased UGT activity is related to an increased number of the thymine-adenine repeats in the promoter region.

Increased enterohepatic circulation of bilirubin (and decreased elimination) occurs if there is a failure to establish breastfeeding or with conditions that result in decreased intestinal motility such as ileus, pyloric stenosis, or intestinal obstruction. In breastfeeding failure characterized by a decreased

feeding frequency, weight loss, and dehydration, there is not only increased enterohepatic circulation but also caloric deprivation.

True breast milk jaundice syndrome develops more gradually, presents typically in the 2nd week of life, and requires the exclusion of other causes of unconjugated hyperbilirubinemia and generally resolves between 1 and 3 months of age. The etiology of breast milk jaundice is unclear but probably multifactorial. Exaggerated enterohepatic circulation, variations in the glucuronidase gene, and variations in the breast milk microbiome have been implicated as factors contributing to the development of breast milk jaundice.

## PATHOGENESIS

### Bilirubin Metabolism

Bilirubin is derived from the catabolism of heme. Approximately, 75% of bilirubin is derived from the breakdown of hemoglobin from senescent red blood cells and the rest from ineffective erythropoiesis and breakdown of hemoproteins, such as cytochromes, myoglobin, nitric oxide synthase, glutathione peroxidase, and catalase.

Heme is degraded in a two step process by the enzyme heme oxygenase resulting in formation of biliverdin and carbon monoxide in equimolar amounts. Carbon monoxide, which diffuses from the cell, binds to hemoglobin in circulating red blood cells to form carboxyhemoglobin (COHb) and is eventually excreted during exhalation (measurable as end-tidal carbon monoxide). Bilirubin is produced from biliverdin by the action of biliverdin reductase, and on entering the circulation, bilirubin binds to albumin and is transported to the liver. Fat-soluble, nonpolar bilirubin crosses the plasma membrane of the hepatocyte and binds to cytoplasmic ligandin, for transport to the endoplasmic reticulum.

Conjugation with glucuronic acid in a reaction catalyzed by UGT transforms bilirubin into a water-soluble form, bilirubin glucuronide, which is easily excretable. Distribution of bilirubin into tissues depends on its binding to albumin and the serum pH. The greater the binding to albumin is and the more alkaline the pH is, the more likely it is that bilirubin will remain in circulation until it enters the liver.

Conjugated bilirubin is excreted into the intestine via the bile, where it is either deconjugated by the enzyme glucuronidase and reabsorbed into the circulation (enterohepatic circulation), or converted by bacteria to nonabsorbable breakdown products. Because the newborn infant has few

intestinal bacteria, the enterohepatic circulation of bilirubin is active in the newborn and contributes to the increased propensity for jaundice.

Although not all full-term infants become visibly jaundiced, nearly all have a higher total serum bilirubin (TSB) concentration (hyperbilirubinemia 1 mg/dL) compared to adults. The range of normal TSB levels in a population depends on race, ethnicity, genetic factors, and rates of breastfeeding. In term, healthy infants, jaundice resolves by 2 weeks of age but may take longer in late preterm infants (35–37 weeks of gestation).

## CLINICAL FEATURES (FIGS. 1 AND 2)

Baby developed jaundice, i.e., indirect type on the 1st day. Baby blood group was O-positive to O-negative mother indicates hemolytic. It is very difficult to differentiate it from physiological type. Damage can occur even with the physiological range of bilirubin level in sick preterm infant. Hence, it is a collective diagnosis.



Fig. 1: A child with pathological jaundice.

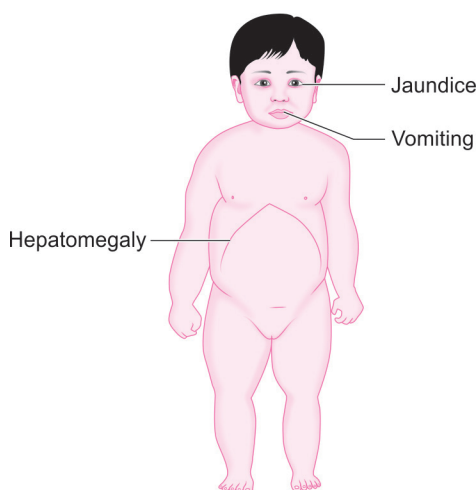


Fig. 2: Clinical features.

### GENERAL FEATURES

- Jaundice
- Not taking feeds
- Convulsion

Pathological jaundice appears before 36 hours of age. The rate of increase of bilirubin levels will be 5 mg/dL/kg/day. Total bilirubin may rise up to 15–20 mg/dL. This may persist for more than 10 days in term babies and for more than 15 days in preterm babies.

In newborns, jaundice is detected by blanching the skin with digital pressure, thus revealing the underlying color of the skin and subcutaneous tissue. This dermal icterus is seen first in the face and then progresses in a caudal manner to the trunk and extremities so that, for a given bilirubin level, the skin of the face will appear more yellow than that of the foot.

The cephalocaudal color difference in newborns is best explained by conformational change in the bilirubin-albumin complex. Following its formation, bilirubin is bound tightly to albumin and the initial binding process is extremely rapid (within 10 ms). This is followed by a train of slow, relaxing changes in the conformation of the bilirubin albumin complex commencing within 1–30 seconds, final conformation being reached 8 minutes after the initial binding. This time course suggests that, initially there is a lower bilirubin-binding affinity to albumin (until the final stage of conformation has occurred) and thus less effective bilirubin-albumin binding in the blood immediately after it has left the reticuloendothelial system. The affinity increases after the blood reaches the distal portions of the body and the conformational changes in the bilirubin-albumin complex are completed.

All pregnant women should be tested for ABO and Rh (D) typing and a serum screen performed for unusual isoimmune antibodies. If such prenatal testing has not been performed, then a direct Coombs test, blood type and an Rh (D) type on the infant's (cord) blood should be done, and this should always be done if the mother is Rh negative. In addition to identification of potentially Rh sensitized infants, this testing is obligatory because it identifies Rh negative mothers who require anti-D globulin to prevent Rh (D) sensitization.

Although there is certainly a wide spectrum of hemolysis in ABO hemolytic disease, this diagnosis generally should not be made unless there

is a positive direct agglutination test and clinical jaundice within the first 12–24 hours. Reticulocytosis and the presence of microspherocytes on the smear help to confirm the diagnosis.

It depends upon the nature of individual immune response. The severity of the illness ranges from mild hemolysis to severe anemia with compensatory hyperplasia of erythropoietic tissue, leading to enlargement of spleen and liver.

Child will be many a time premature. Any evidence of IUGR should be looked for. Associated features of polycythemia and in utero infection should be looked for. Microcephaly may be present with toxoplasmosis, other (congenital syphilis and viruses), rubella, cytomegalovirus and herpes simplex virus (TORCH) infection. Presence of pallor suggests hemolytic type of anemia. This diagnosis is supported by hepatosplenomegaly. Features of omphalitis and hypothyroidism should be looked for.

The profound anemia results in pallor, sign of cardiac decompensation, i.e., cardiomegaly and respiratory distress, massive anemia and circulatory collapse. This leads to excessive abnormal fluid in two or more fetal compartments, i.e., skin, pleura, pericardium, termed as hydrops fetalis. It frequently results in death in utero or shortly after the birth.

The severity of hydrops is related to the level of anemia and the degree of reduction in serum albumin. This is due to hepatic dysfunction. Petechiae, purpura and thrombocytopenia may also be present in severe cases.

#### ESSENTIAL DIAGNOSTIC POINTS

- Clinical jaundice in first 24 hours of life
- Total bilirubin increasing by more than 5 mg%/day
- Total serum bilirubin more than 12.9 mg% in full term
- Direct bilirubin more than 2 mg%
- Clinical jaundice persisting for more than 1 week in full term and more than 2 weeks in preterm infants
- It is clinically appreciated with bilirubin values of 7 mg%
- Babies with asphyxia, acidosis, hypoglycemia, preterm infant are at higher risk bilirubin encephalopathy

Icterus is generally evident on the 1st day of life. This is because the infants bilirubin conjugating and the excretory system are unable to cope with the load resulting from massive hemolysis. Indirect bilirubin accumulates postnatally. It may rapidly reach extremely high levels. This represents significant risk of bilirubin encephalopathy. Hypoglycemia occurs more frequently in infants with severe hemolytic disease.

## Infants with Severe Jaundice

In those infants with severe jaundice (TBS levels greater than 18 mg/dL), it is worth looking for ABO immunization and other causes of hemolysis. If ABO or some other type of hemolytic disease is strongly suspected, these infants generally require more aggressive therapy than those with nonhemolytic jaundice. In the absence of hemolysis and any abnormal historical or physical findings, jaundice by itself is almost never a sign of serious illness and although, some reports have suggested that unexplained indirect hyperbilirubinemia may be the only manifestation of sepsis in otherwise healthy appearing newborns.

## Prolonged Jaundice (Beyond 3 Weeks)

This is persistence of significant jaundice (10 mg/dL) beyond 3 weeks in a term baby. The common causes include inadequate feeding, breast milk jaundice, cephalohematoma hemolytic disease, glucose 6-phosphate dehydrogenase (G6PD) deficiency and hypothyroidism. Urinary tract infection should be considered.

## Danger Signs in Jaundiced Infants

- Family history of significant hemolytic disease
- Onset of jaundice in first 24 hours of life
- Onset of jaundice after 3 days of life
- Vomiting
- Lethargy
- Poor feeding
- Fever
- High-pitched cry
- Dark urine
- Light stools

Every infant who is jaundiced beyond 3 weeks of age must have a measurement of direct bilirubin performed. If the level is elevated, the urine should be tested for bile and the stool color evaluated. This approach is essential for the early identification of infants with biliary atresia. If these infants are to benefit from the operation of portoenterostomy, surgery should be performed before 60 days of age. If an elevated direct bilirubin measurement is obtained while the infant is in the nursery, it must be repeated; if it remains elevated, the infant must be investigated for possible causes of cholestatic jaundice.

## DIAGNOSIS

Evaluation of a jaundiced infant should try to identify the type of hyperbilirubinemia (indirect or direct),



its severity, the risks of bilirubin encephalopathy, and the cause of the hyperbilirubinemia.

A review of the maternal, family, and infant history should aim to identify blood group incompatibilities, congenital infections, maternal diabetes, maternal drugs, birth trauma, closed space bleeding in the newborn, familial causes such as hereditary spherocytosis, G6PD deficiency, family history of liver disease, and siblings with jaundice (which may suggest blood group incompatibilities, breast milk jaundice, or Lucey-Driscoll syndrome). The newborn should be assessed for poor feeding, decreased stooling or urination, excessive weight loss, and poor breastfeeding or poor milk intake.

Physical examination of the infant should try to identify whether the infant is preterm, small for gestational age, or large for gestational age. The infant should be assessed for ruddiness (suggestive of polycythemia), pallor, presence of extravasated blood (e.g., cephalohematoma), petechiae, hepatosplenomegaly, chorioretinitis, omphalitis, evidence of sepsis, and features of congenital hypothyroidism. Finally, careful examination and documentation should be made of features of bilirubin encephalopathy.

Visual inspection of the degree of yellow discoloration of the skin is unreliable, and a total serum bilirubin level should be obtained. Other common laboratory tests to identify the presence of hemolysis and its etiology and severity may be indicated. These include a maternal and infant ABO and Rh blood types, indirect and direct antiglobulin test, complete blood count, reticulocyte count, peripheral blood smear, a G6PD level, and if necessary, specific tests such as an osmotic fragility test. Finally, assessment of serum albumin, and if the infant appears ill, the blood pH may be helpful to assess the risk of bilirubin encephalopathy (**Table 1**).

Evaluation for infection may be warranted depending on the history and physical examination. ABO hemolytic disease is the most common form of hemolysis diagnosed in the newborn.

Only half of those infants with a positive direct antibody (Coombs) test are likely to have significant hemolysis. On the other hand, some infants with a negative direct Coombs test have increased rates of hemolysis. Reticulocytosis and the presence of microspherocytes on a peripheral blood smear may help confirm the diagnosis but are not pathognomonic.

Routine testing for G6PD deficiency is indicated when family history or ethnic or geographic origin suggests the likelihood of G6PD deficiency. However, not all infants with G6PD deficiency have hemolysis, and G6PD levels can be high in the presence of hemolysis. Also, such testing is not available currently in all institutions and, when done, the results are usually not timely enough for immediate decision making. Careful follow-up is required for all discharged newborn infants who have hemolysis.

Transcutaneous bilirubinometry has been investigated as a substitute for serum bilirubin assessment. Noninvasive transcutaneous bilirubin (TcB) measurements have been shown to underestimate TSB measurements, especially with advancing chronological age.

If an infant is significantly jaundiced clinically, it is prudent to immediately institute phototherapy while waiting for the laboratory test results. If the serum bilirubin exceeds thresholds described in published guidelines, then phototherapy should be continued and periodic serum bilirubin assessments performed until the bilirubin drops below the phototherapy threshold.

All the neonates with the icterus warrant the investigation. The clinical and biochemical jaundice asks for detailed investigation. This is enlightened as follows:

- **Clinical jaundice:**
  - Early onset, i.e., within 24 hours
  - Sick infant
  - Persistent jaundice more than a week at term and more than 2 weeks at preterm babies

**TABLE 1:** Guidelines for initial evaluation and follow-up of jaundice in apparently healthy term and near term infants.

<i>Clinical observation</i>	<i>Initial actions</i>	<i>Other evaluations</i>	<i>Follow-up</i>
Onset of jaundice in first 24 hours	Clinical evaluation Measure TSB and TcB	Blood group (ABO, Rh) Direct Coombs test CBC, smear for red cell morphology, reticulocyte count	Repeat TSB in 4–24 hours
Onset of jaundice 24–72 hours	Clinical evaluation Assess cephalocaudal distribution TcB	TSB if indicated by TcB or clinical evaluation	Clinical evaluation and/or TcB or TSB within 24–72 hours and repeat as necessary

- *Biochemical jaundice:*
  - Rising bilirubin, i.e., more than 5 mg/dL/day
  - Conjugated serum bilirubin more than 1.5 mg/dL
  - Conjugated hyperbilirubin more than 2 mg/dL
  - To the serum bilirubin level more than 18 mg/dL in a term at the 3–5 days in premature infants 12–15 mg/dL.

These help to know the severity of the icterus and helps in the management. These are classified and investigations are again dependent on the time of onset of jaundice. These are depicted here.

- *Onset within 24 hours:*
  - Serum bilirubin
    - ♦ Conjugated
    - ♦ Unconjugated
  - Total count and differential count
  - Blood group and typing
  - Coombs test
- *Onset after 24 hours:*
  - Serum bilirubin
  - Blood group and typing
  - Coombs test
  - Urine culture and sensitivity
  - Total count and differential count
  - Blood culture and sensitivity
  - G6PD
- *Prolonged jaundice:*
  - Serum bilirubin
  - Thyroid function test
  - Liver function test
  - Urine culture and sensitivity
  - Total count and differential count
  - G6PD
  - Blood culture and sensitivity
  - *Others:* Sepsis screen; thyroid function test; urine for reducing substances to rule out galactosemia; specific enzyme/genetic studies for Crigler-Najjar syndrome, Gilbert syndrome and other genetic enzyme deficiencies.

#### LABORATORY SALIENT FINDINGS

- Serum bilirubin direct and indirect
- Blood grouping of the mother and child ABO and Rh
- Direct Coombs in infant
- Hematocrit
- Peripheral blood smear RBC morphology and reticulocyte count

### Rh Isoimmunization

Hemolytic disease of newborn results from transplacental passage of the maternal antibody active

against red blood cell (RBC) antigens of the infant. This leads to increased rate of RBC destruction. It is the important cause of pathological jaundice in newborn.

The Rh antigenic determinants are genetically transmitted from each parent and determine the Rh type. This will direct production of the number of blood group factors.

When Rh-positive blood is infused into Rh-negative women, or Rh-positive fetal blood containing D antigen inherited from an Rh-positive father enter the maternal circulation during pregnancy, with spontaneous or induced abortion or at delivery, this leads to antibody formation against the D may be induced in inseminated Rh-negative recipient mother. Hemolytic disease rarely occurs during first pregnancy. This is because transfusion of Rh-positive fetal blood into an Rh-negative mother tends to occur near the time of delivery.

### Hemolytic Disease

The combination of antepartum and postpartum prophylaxis with Rh immunoglobulin has dramatically reduced the incidence of erythroblastosis fetalis and the contribution of ABO hemolytic disease to neonatal jaundice was discussed in the section on laboratory evaluation. Other hemolytic processes to be considered include spherocytosis and other morphologic abnormalities of the erythrocyte, in addition to the erythrocyte enzyme deficiencies.

Infants with G6PD deficiency have an increased rate of red cell breakdown and bilirubin production, in those who develop significant hyperbilirubinemia, the major problem appears to be abnormal bilirubin elimination.

The risk of kernicterus in G6PD deficient infants with TSB levels above 20 mg/dL (342 mmol/L) appears to be comparable to that associated with Rh disease. Thus, in the presence of G6PD deficiency, more aggressive treatment of these infants probably is indicated.

### Antenatal Diagnosis

The presence of measurable antibody titer of 1:64 or greater suggests significant hemolytic disease. Although exact titer correlates poorly with severity of the disease. If the mother is found to have antibody against D at a titer of 1:16 or greater at any time during subsequent pregnancy, the severity of the fetal disease should be monitored by amniocentesis, percutaneous umbilical blood sampling (PUBS), and ultrasonography.

Real-time ultrasonography is used to detect progression of the disease.

Amniocentesis is used to assess fetal hemolysis. Hemolysis of the fetal RBCs produces hyperbilirubinemia before onset of severe anemia. Bilirubin is cleared by placenta. But significant proportion enters the amniotic fluid. This can be measured by spectrophotometry. Amniocentesis is performed if there is evidence of maternal sensitization (titer  $\geq 1:16$ ). Spectrophotometric scanning of amniotic fluid wavelengths demonstrates a positive optical density, and deviation of absorption for bilirubin from normal at 450 nm. The optical density 1450 is a reflection of the fetal bilirubin level and thus hemolysis and indicates severity of anemia and risk of intrauterine deaths.

### *Postnatal Diagnosis*

Immediately after birth of any infant to Rh-negative mother, blood from umbilical cord or from infant should be examined for ABO blood group, Rh type, hematocrit and hemoglobin. Coombs test should be done. If Coombs test is positive, baseline serum bilirubin should be measured. Direct Coombs test will result in strongly positive in clinically affected infants. It may remain there for months.

### **Kernicterus**

Acute bilirubin encephalopathy caused by unconjugated bilirubin in the infant presents with a poor suck, lethargy, hypotonia in the first 2 days of age followed by hypertonia of extensor muscles, opisthotonus, retrocollis, and fever in the middle of the 1st week and hypertonia after the 1st week. Surviving infants may have exaggerated deep tendon reflexes, obligatory tonic neck reflexes, delayed motor skills, and after the 1st year, movement disorder (choreoathetosis, ballismus, tremor), upward gaze, paralytic palsies, intellectual deficits, and sensorineural hearing loss.

Kernicterus is characterized pathologically by staining and necrosis of neurons in the basal ganglia, hippocampus, and subthalamic nuclei of the brain. Those regions most commonly affected are the basal ganglia, particularly the subthalamic nucleus and the globus pallidus; the hippocampus, the geniculate bodies, various brainstem nuclei, including the inferior colliculus, oculomotor, vestibular, cochlear and inferior olivary nuclei; and the cerebellum, especially the dentate nucleus and the vermis. Magnetic resonance imaging of infants with kernicterus has shown abnormalities in these regions. Bilirubin may also cause changes in

brainstem-evoked responses and abnormal infant cry in the acute phase, and sensorineural hearing loss long term.

Neuronal necrosis is the dominant histopathologic feature after 7–10 days of postnatal life. For the most part, its distribution corresponds with the distribution of bilirubin staining, although there are some exceptions to this rule. Intense staining develops in the olivary and dentate nuclei, but there is little neuronal necrosis in these regions. The important areas of neuronal injury (as opposed to staining) include the basal ganglia, brainstem oculomotor nuclei, and brainstem auditory pathways, especially (cochlear) nuclei.

Pathogenesis is a complex process, it is related to interaction between the level of bilirubin, gestational maturity and integrity of blood-brain barrier.

Serum bilirubin and protein ratio more than 3.5 will be associated with brain damage.

The classical neurological signs are not seen at prematurity. Here bilirubin staining is limited to cranial nerves, subthalamus and thalamus.

The inhibition of protein phosphorylation is probably an important mechanism in bilirubin toxicity and lysine binding may have an important role in the mediation of this toxicity.

It is not known why bilirubin is deposited preferentially in the basal ganglia, but it is possible that it may first attach to nerve terminals, thus lowering membrane potentials and decreasing nerve conduction and after further exposure, may penetrate nerve terminals or axons with retrograde uptake of bilirubin in the cell body.

Albumin has a primary binding site with the capacity for binding up to 1 molecule of bilirubin per molecule of albumin and one or more binding sites with much lower affinities. When the bilirubin-albumin ratio exceeds 1, the concentration of free or unbound bilirubin increases, but binding at the lower affinity sites continues up to a molar bilirubin-albumin ratio of 3:1. It has been widely accepted that bilirubin toxicity occurs when free bilirubin enters the brain and binds to cell membranes.

No association can be made between a specific serum bilirubin level duration of exposure to high bilirubin levels and the risk of neurotoxicity, although the risk is higher with a serum bilirubin level of greater than 25 mg/dL. Low serum albumin levels and the use of agents that displace bilirubin from albumin such as sulfisoxazole, benzyl alcohol, or ceftriaxone, can increase the risk of bilirubin encephalopathy. A decrease in blood pH

may render unbound (free) bilirubin lipophilic, thereby enhancing tissue uptake.

Premature infants are particularly at risk of encephalopathy because of low serum albumin concentrations and frequency of acidosis. Albumin-bound bilirubin and conjugated bilirubin do not cross the blood-brain barrier but when the barrier is disrupted, as in prematurity, asphyxia, meningitis, sepsis, and intracranial hemorrhage, bilirubin may access vulnerable areas of the developing brain.

*Blood-brain Barrier*

A blood-brain barrier exists that limits the entry of certain substances into the central nervous system. This barrier, at the cerebral blood vessels, is due to a continuous lining of endothelial cells connected by tight junctions that restrict intercellular diffusion. The blood-brain barrier normally excludes most water-soluble substances and proteins but is permeable to lipid-soluble substances that are not protein bound. Large molecules, such as albumin, are excluded from the brain but may enter when the brain is made permeable by the infusion of a hypertonic solution.

Opening of a blood-brain barrier allows albumin bound bilirubin to bathe the neurons, but whether or not free bilirubin binds to albumin or to cellular membranes may be determined by the binding of bilirubin to albumin.

In the first few days, the infant becomes lethargic and hypotonic and sucks poorly. Later in the 1st week, the second phase evolves. The infant becomes hypertonic and frequently develops a fever and a high-pitched cry. The hypertonia involves the extensor muscle groups, and most infants exhibit backward arching of the neck (i.e., retrocollis) and trunk (i.e., opisthotonus). The fever may be due to diencephalic involvement. In the third phase, usually after 1 week, hypertonia subsides and is replaced by hypotonia. Infants who manifest hypertonia during the second phase invariably develop the clinical features of chronic bilirubin encephalopathy.

*Extrapyramidal Disturbances*

Athetosis (i.e., involuntary, sinuous, writhing movements) may develop as early as 18 months but may be delayed as late as 8 or 9 years. If sufficiently severe, athetosis may prevent useful limb function. These movements are described as uncontrollable, purposeless, involuntary and incoordinate. They may be rapid and jerky (choreiform), slow and worm-like (orthodox athetosis) or so slows by

hypertonicity that the patient may assume shortly fixed attitudes with stiffness of the extremities (dystonia). Severely affected children also may have dysarthria, facial grimacing, drooling and difficulty in chewing and swallowing.

*Auditory Abnormalities*

Some degree of hearing loss is often found in children with chronic bilirubin encephalopathy. Pathologic studies and studies of brainstem auditory evoked response (BAER) indicate that injury to the brainstem, specifically the cochlear nuclei, is the principal cause of hearing loss, although occasional studies suggest possible involvement of the peripheral auditory system as well.

Hearing loss is generally most severe in the high frequencies and an association between moderate hyperbilirubinemia and subsequent sensorineural hearing loss has been described in low birth weight infants.

*Gaze Abnormalities*

Limitation of upward gaze and other gaze abnormalities occur, and that full vertical eye movements during the Doll's eye maneuver are attained in most affected children suggests that the lesion is above the level of the oculomotor nuclei. Some patients have paralytic gaze palsies. Supranuclear palsies can be explained by bilirubin deposition. And neuronal injury in the rostral mid-brain, and nuclear palsies can be explained by damage to the oculomotor nuclei.

Organs stained by bilirubin in kernicterus	
• Basal Ganglia	• Putamen
• Globus pallidus	• Caudate nucleus

The serum bilirubin level again varies to produce early symptoms in kernicterus. This can be called symptomatic levels displayed in **Box 1**.

The precise level of bilirubin at which brain damage occurs is uncertain. There are many other factors responsible for kernicterus. These are called risk factors and are placed in **Box 2**.

*Clinical Classification of Kernicterus*

Kernicterus can be classified clinically as follows:

- *State I:* Decreased tone, lethargy, poor feeding, vomiting, poor Moro reflex
- *State II:* Opisthotonus, seizures, fever, rigidity, oculogyric crisis
- *State III:* Spasticity at about 1 week of age
- *State IV:* Late sequela

**BOX 1: Symptomatic levels for kernicterus.**

Term	: 25–30 mg/dL
Rhesus	: 20–25 mg/dL
Preterm	: 10 mg/dL

**BOX 2: Risk factors for kernicterus.**

• Less than 2 weeks old	• Prematurity
• Displacement of bilirubin from albumin	• Acidosis
• Infection	• Asphyxia
• Hypothermia	• Drugs—diazepam, sulfonamide
• Excessive hemolysis	• ABO incompatibility
• Rh incompatibility	• Septicemia
• Congenital spherocytosis	

**Biochemical and Biological Determinants or Bilirubin Encephalopathy**

**Bilirubin level:** In term baby, serum bilirubin should not be allowed to cross 25 mg/dL. There is no safe level in babies. Every attempt should be made to see that serum bilirubin level should not cross 1 mg/dL/100 mg.

**Bilirubin-protein ratio:** Bilirubin-protein ratio of 3:5 or more may be associated with development of bilirubin encephalopathy.

**Blood-brain barrier:** Gestational immaturity, hypoxia, hypoglycemia, acidosis, birth injury and septicemia.

**Salicylate saturation index:** It determines the extent to which albumin is saturated with bilirubin. This can be assessed by displacement or addition of salicylate in vitro. Salicylate index of 8 or more is associated with bilirubin encephalopathy.

**TREATMENT (TABLE 2)****Mechanisms and Principles**

Hyperbilirubinemia can be treated by exchange transfusion, which removes bilirubin mechanically. Phototherapy, which converts bilirubin to products that can bypass the liver's conjugating system and be excreted in the bile or in the urine without further metabolism; and pharmacologic agents that interfere with heme degradation and bilirubin production, accelerate the normal metabolic pathways for bilirubin clearance or inhibit the enterohepatic circulation of bilirubin. Phototherapy is the most common treatment in use for hyperbilirubinemia; exchange transfusions generally are reserved for phototherapy failures.

**TABLE 2: Management of hyperbilirubinemia in the healthy term and near-term newborn.**

TSB level [mg/dL (μmol/L)]				
Age (h)	Consider photo-therapy	Photo-therapy	Exchange transfusion if intensive photo-therapy fails	Exchange transfusion and intensive photo-therapy
≤24	–	–	–	–
25–48	≥12 (205)	≥15 (260)	≥20 (340)	≥25 (430)
49–72	≥15 (260)	≥18 (310)	≥25 (430)	≥30 (510)
≥72	≥17 (290)	≥20 (340)	≥25 (430)	≥30 (510)

The bilirubin levels at which intervention is necessary, is still a contentious issue.

**Phototherapy**

Phototherapy is thought to modify bilirubin deposited within the first few millimeters of the skin surface. It should not be used with the child with liver disease or obstructive type of jaundice. Because this causes the retention of products of phototherapy, this may cause bronze baby syndrome. In such situation, the exchange transfusion is the safer method of treatment (**Box 3**).

**Indications for Phototherapy**

- Abnormal rise in bilirubin level
- Prophylactic therapy in premature with jaundice
- Hemolytic disease in newborn impending for exchange transfusion
- Serum bilirubin more than 16–17 mg/dL on day 4
- Nonhemolytic type of jaundice with bilirubin level more than 15 mg/dL on day 4

Laboratory investigation such as serum bilirubin can also be considered as cut off point for phototherapy.

Weight of the infant	Serum bilirubin level
<1,500 g	5 mg/dL
1,500–2,000 g	8–12 g/dL
2,000–2,500 g	13–15 mg/dL
Full term	15–20 mg/dL

**Mechanism of Action in Phototherapy**

It helps to understand how phototherapy works if we consider that light is an infusion of discrete



**BOX 3:** Factors that determine dose of phototherapy.

- Spectrum of light emitted
- Irradiance of light source
- Design of phototherapy unit
- Surface area of infant exposed to the light
- Distance of infant from light source

photons of energy that correspond to the individual molecules of a drug in a conventional medication. Absorption of these photons by bilirubin molecules in the skin leads to the therapeutic effect in much the same way as binding of drug molecules to a receptor has a desired effect.

### Light Spectrum

The spectrum of light delivered by the phototherapy unit is determined by the type of light source and any filters used. Because of the optical properties of bilirubin and skin, the most effective lights are those with wavelengths that are predominantly in the blue green spectrum.

Photoisomerization occurs when bilirubin is exposed to light. This occurs in extravascular space of the skin. This leads to conversion of bilirubin to bilirubin isomer, i.e., lumirubin. This isomer diffuses into the blood and bound to albumin. Later it is transported to the liver. It is excreted with the bile in the bowel. Here it may be converted back into unconjugated bilirubin.

*Intramolecular cyclization of bilirubin to lumirubin:* It is rapidly excreted in the bile and urine. It is the most important pathway to lower serum bilirubin level.

*Photo-oxidation:* Bilirubin is converted to pale colored product. They are excreted in urine.

Bilirubin absorbs the light in 400–500 nm range. Irradiation in this range will be more effective. White lamps with peak out at 425–475 nm are more effective. White lamps with peak at 550–600 nm are also effective. The range of 380–700 nm of white lamp is adequate for treatment.

### Technique of Phototherapy

The source of light is four white light and four blue light. The length of the fluorescent lamp is 18 inches. These should be 45 cm above the infant. The shield made of plexiglass may be used. This screens out the wavelength below 300 nm. Hence, less harm to child. Eyes and external genitalia should be covered by eye patch and diaper. Posture of infant should be changed every 2 hourly.

Child should be weighed daily, extra fluid should be given. Bilirubin level should be monitored every 12th hourly. Once it begins to fall, the phototherapy can be stopped. Sometimes it may be restarted if the bilirubin level is not low.

### Side Effects of Phototherapy

*Insensible water loss:* This is more common among preterm infants. These children should be given extra fluid. The extra amount is 30 mL/kg/day. This may not be required in full term baby who is taking feeds well.

- *Hypocalcemia*
- *Loose green stool:* There will be increased fetal water loss. The cause is thought to be increased bile salts and unconjugated bilirubin in guts. This produces changes in the bacterial flora. Hence, these children should be fed with lactose free until phototherapy is stopped.
- *Skin may be erythematous:* Because of the hyperemia or increased blood circulation.
- *Retinal damage:* Occurs if the phototherapy is given without covering the eyes. This leads to visual defects.
- *Bronze baby syndrome:* This occurs if the phototherapy is given to the infants with obstructive jaundice. In obstructive jaundice, there will be accumulation of the photooxidized isomerase and this is called bronze baby syndrome.
- *Cellular damage:* This includes chromatid exchange and DNA strand breakages. It may be necessary to cover scrotum.

### Phenobarbitone

The dose of phenobarbitone is 5–8 mg/kg/body weight every 24 hours. This induces microsomal enzyme in the liver. This increases bilirubin conjugation and excretion. It takes 3–7 days to become effective and may take much longer time in premature babies. Phenobarbitone can be used in type II Crigler-Najjar syndrome. It cannot be used for prophylactic purposes.

### Contradictions of Phototherapy

- Significantly elevated direct bilirubin
- Family history of prophyrias
- Loss of rods and cones in retina

Discontinue phototherapy once two TSB values 12 hours apart are below current age-specific cut offs. The infant should be monitored clinically for rebound bilirubin rise within 24 hours for babies with hemolytic disorders.

## Exchange Transfusion (Table 3)

It reduces the level of bilirubin effectively. Indications for exchange transfusion are listed in **Box 4**.

The procedure will correct anemia, congestive cardiac failure in hydrops. These children would have already received intrauterine transfusion. Rebound of bilirubin after the exchange is expected because of sequestered sensitized RBCs and hemolysis of transfused RBCs.

### Technique

The sick neonate should be stable before starting on exchange transfusion. This includes control of asphyxia, hypoglycemia, acidosis and temperature. Cardiac monitor and blood pressure cuff should be placed. Intravenous line is maintained for glucose and medications. Blood glucose, serum potassium and pH should be measured.

If the umbilical cord is old and dried, it can be softened by soaking in saline water for half an hour. This makes insertion of catheter easier. Catheter is inserted as far as required for free exchange. The position of the venous catheter should be left open for the risk of air embolism.

Purse string silk suture should be placed after the completion of exchange transfusion. The tie around the cord should be tightened for 1 hour. This is to avoid necrosis of skin. Venous catheter should be pulled out quickly to check the blood from the distal end.

If the umbilical vein catheterization is not possible, exchange transfusion can be carried out by central vein placed through the anterior cubital fossa.

**TABLE 3:** Serum bilirubin for exchange transfusion.

Birth weight	Serum bilirubin
<1,250 g	13
1,250–1,499 g	15
1,500–1,999 g	17
2,000–2,499 g	18
More than 2,500 g	20

### BOX 4: Indications of exchange transfusion

- Severe nonhemolytic anemia
- Septicemia with sclerema
- Cord bilirubin level more than 5 mg
- Chronic anemia
- Disseminated intravascular coagulation
- Hypoxemia in RDS
- Cord hemoglobin level less than 10 mg/mL
- Indirect serum bilirubin level 20 mg/100 mL
- Acute renal hepatic failure

It is a common practice to administer calcium during exchange transfusion to citrate phosphate dextrose (CPD) anticoagulated blood. The citrate present in the blood can bind calcium and magnesium. This produces decrease in these ions.

Albumin infusion has been proposed 1–2 hours before exchange transfusion. During the process, attempt will be made to remove the bilirubin in hastened way. Albumin may draw the tissue bound bilirubin into the circulation.

Albumin should be administered with caution in infants with respiratory distress and congestive heart failure.

*Isovolumetric exchange transfusion:* It is done in a small sick and hydropic children. Here blood is pulled out of umbilical arteries and simultaneous blood is pushed in umbilical vein.

*Two-volume exchange:* This usually involves the double the blood volume of the infant's blood. The blood of an infant is 80 mL/kg. Therefore, exchange transfusion uses 160 mL/kg of the blood.

In the procedure, the blood is removed in aliquots that are tolerated by infants. The amount of the blood removed depends upon the weight of the infants.

1,500 g	5 mL
1,500–2,500 g	10 mL
2,500–3,500 g	15 mL
3,500 g or more	20 mL

### Blood volume removed by exchange

1. Volume exchange 63%
2. Volume exchange 87%
3. Volume exchange 95%

Anemic sick children should be given partial exchange transfusion with packed cells, i.e., 25–80 mL/kg. This will raise hematocrit to 40%. The recommended time of exchange transfusion is 1 hour. Blood should be shaken well after every deciliter of exchange. This avoids the sedimentation of RBCs. Phototherapy should be continued after the exchange transfusion.

### Complications of Exchange Transfusion

- Electrolyte imbalance
- Cardiac problem—cardiac arrest, arrhythmias and volume overload
- Vascular—air embolism, thrombosis, infarction
- Bleeding—thrombocytopenia, deficient clotting factor
- Infection—septicemia, hepatitis, CMV, AIDS
- Metabolic—hypoglycemia, hypocalcemia, hypercalcemia, acidosis.

## Supportive Treatment

*Adequate feeding:* Hydration should be maintained and hypoglycemia should be prevented. This is done by early feeding. Early feeding helps in building up of bacterial flora. This reduces enterohepatic circulation.

*Aspiration of cephalohematoma:* Cephalohematoma will also cause severe jaundice in newborn. Here aspiration of the cephalohematoma should be done, as it is the root cause of jaundice.

*Treatment of sepsis and hepatitis:* Septicemia will present with jaundice in newborn. Septicemic workup and treatment with suitable antibiotics should be done.

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# Normal Newborn

## PRESENTING COMPLAINTS

A newborn child was brought for general check-up.

### History of Presenting Complaints

A newborn baby was brought to pediatric outpatient department for general check-up. Mother had delivered the baby in primary health center in village. This baby was the first sibling of consanguineous marriage. Mother had antenatal check-up in the primary health center. She was having regular check-up and had received immunization as per the advice. Antenatal health check-up investigations were within normal range.

She went to the primary health center with the delivery pain and there was drainage of the amniotic fluid. Fluid was clear. She delivered vaginally with vertex presentation. The delivery was conducted by the sister. Baby cried immediately after the delivery. Cry of the baby was good. Neonatal reflexes were satisfactory. Baby was put to breast immediately. Baby started to take the

feeds regularly. Later the baby was sent to pediatric OPD the next day for general check-up.

## EXAMINATION

Newborn child was moderately built and moderately nourished. Baby was active, alert, and was crying. The anthropometric measurements included, the weight of the child was 3 kg (50th centile), length was 51 cm (75th centile) and the head circumference was 35 cm.

Child was afebrile, the heart rate was 140 per minute the respiratory rate was 24 per minute. Blood pressure was 50/40 mm Hg, there was no pallor, acrocyanosis was present, no edema, and no lymphadenopathy.

Neonatal reflexes (NNR) were satisfactory. Anterior fontanelle was normal, skin and spine were normal. There were no clinically evident congenital anomalies. The baby was appropriate-for-gestational age.

Cardiovascular system revealed first and second heart sounds heard. No murmur—suggestive of congenital heart disease. Respiratory system revealed presence of crepitation and rhonchi. Per abdomen examination showed mild distension of the abdomen. There was no significant organomegaly. Bowel sounds were normal.

## INVESTIGATION

Hemoglobin	: 14 g/dL
TLC	: 1,23,000 cells/cu mm
DLC	: $P_{72} L_{24} E_2 M_2$
Blood culture and sensitivity	: Sterile
Urine culture sensitivity	: Sterile
Blood group and Rh typing	: O +ve
Chest X-ray	: NAD

## DISCUSSION

It includes history taking and physical examination. History dates from the day of conception till

### CASE AT A GLANCE

#### Basic Findings

Weight	: 3 kg (50th centile)
Length	: 51 cm (75th centile)
Temperature	: 37°C
Pulse rate	: 140 per minute
Respiratory rate	: 24 per minute
Blood pressure	: 50/40 mm Hg

#### Positive Findings

##### History

- FTND
- Delivered in PHC
- Antenatal care was present

##### Examination

- Normal child
- NNR satisfactory
- No evidence of congenital anomaly

##### Investigation

- Normal

the delivery, and also few days after the delivery. Birth history includes antenatal, natal and post-natal events. Family history of other sibling should also be ascertained.

Antenatal history includes previous obstetric history, number of gravida and para. History suggestive of abortion and stillbirth should be sought. Chronic disease of the mother such as cardiac disease, tuberculosis, and hypertension should be ascertained. History of any drug intake, and antenatal investigation should be noted.

Natal history includes birth of the child. Mode of delivery, place of the delivery, presentation of the baby, direction of the labor should be ascertained.

In postnatal history birth asphyxia should be noted down. Apgar scoring at 1 minute and 5 minutes should be sought. History of passing of urine and meconium should be ascertained. Presence of jaundice and time of onset of jaundice should be noted.

The neonatal examination is best performed in an appropriately equipped, well lit, warm, draft-free room, with the parents present. Examining the infant under a servo-controlled radiant warmer is an alternative. Thorough hand-washing before and after handling each infant is essential to prevent the spread of pathogenic organisms, and if the infant has not had a first bath, gloves should be worn.

Isolated minor congenital anomalies are quite common, with some studies reporting these in as many as so of the newborn population, but the presence of three or more increases the risk of the infant having a syndrome. Evidence of trauma in part of the baby should lead to a search for trauma in other areas, particularly in large infants and in infants who underwent difficult deliveries such as breech or forceps delivery. It is also important to be able to distinguish malformations from deformations as the etiology and managements differ.

Gestational Age Assessment (Table 1)

The infant’s gestational age should be estimated and body size compared with appropriate normal standards. There are several ways to estimate gestational age, including reliable maternal history, prenatal ultrasound scan performed before 20 weeks of gestation, and physical examination of the infant’s skin, external genitalia, ears, breasts, and neuromuscular behavior. Infants are classified as preterm (born at less than 37 completed weeks of gestation), early term (37–38 weeks), term (39–41 weeks), and post-term (>42 weeks).

Birth weight, head circumference, and length should be measured. Length is measured from vertex to heel with the infant’s legs fully extended.

TABLE 1: Gestational age assessment.

<i>Skin</i>	<i>Sticky, friable, transparent</i>	<i>Gelatinous red, translucent</i>	<i>Smooth pink, visible veins</i>	<i>Superficial peeling and/or rash, few veins</i>	<i>Cracking pale areas rare veins</i>	<i>Parchment, deep cracking, no vessels</i>	<i>Leathery, cracked, wrinkled</i>
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40–50 mm to 1 cm	<5 mm no crease	Faint red marks	Anterior transverse crease only	Creases ant 2 to 3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola no bud	Stippled areola 1–2 mm bud	Raised areola 3–4 mm bud	Full areola 5–10 mm bud	
Eye/ear	Lids fused loosely 1 tightly 2	Lids open Pinna flat Stags folded	Sl. Curved pinna, soft slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm, instant recoil	Thick cartilage ear stiff	
Genitals (male)	Scrotum flat smooth	Scrotum empty faint rugae	Testes in upper canal rare rugae	Testes descending few rugae	Testes down good rugae	Testes pendulous deep rugae	
Genitals (female)	Clitoris prominent	Prominent clitoris, small labia minora	Prominent clitoris enlarging minora 3	Majora and minora equally prominent	Majora large minora small	Majora cover clitoris and minora	



These measurements are then compared for gestational age against standard population-based growth charts. An infant is considered to be appropriate for gestational age (AGA) if the birth weight for gestational age falls between the 10th and 90th percentile. Twenty percent of infants with serious congenital malformations are small for gestational age.

Two methods that are commonly used clinically for the assessment of gestational age are: Parkin method and new Ballard method.

Gestational age assessment again depends on skin texture, skin color, breast size and breast firmness.

### Skin Texture

Skin texture is tested by picking up the fold of abdominal skin between fingers and thumb and by inspection.

#### Score

- 0 - Very thin and gelatinous feel
- 1 - Thin and smooth
- 3 - Slight thickening and stiff feeling
- 4 - Thick and parchment-like with superficial or deep cracking

### Skin Color

- 0 - Dark red
- 1 - Uniformly pink
- 2 - Pale pink
- 3 - Pale

### Breast Size

Measured by feeling the breast nodule by finger and thumb

- 0 - No breast tissue palpable
- 1 - Not more than 0.5 cm in diameter
- 2 - 0.5–1 cm in diameter
- 3 - More than 1 cm in diameter

### Ear Firmness

Tested by palpation and folding of the upper pinna and notching and recoiling

**Score 0:** Pinna feels soft and is easily folded in bizarre position without springing back into position spontaneously.

**Score 1:** Pinna feels softer along the edge and easily folded and return slowly to the correct position spontaneously.

**Score 3:** Pinna firm with definite cartilage extending up to the periphery and springs back immediately into the position after being folded.

#### BOX 1: Maturity rating—Parkin method.

<i>Parkin score</i>	<i>Age (in weeks)</i>
1	26
2	30
3	33
4	34
5	35
6	36
7	37
8	38
9	39
10	40
11	41
12	42

#### BOX 2: Maturity rating—Ballard method.

<i>Ballard score</i>	<i>Age (in weeks)</i>
−10	20
−5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Maturity rating is calculated as given in the **Boxes 1 and 2**.

## GENERAL PHYSICAL EXAMINATION

All the babies should however be examined in more detail by pediatrician preferably within 24 hours. The baby should be at least 6-hour-old before preliminary detailed examination. However, the examination of the child should be conducted usually for three times, i.e.

1. At birth
2. After 24 hours
3. At the time of discharge

The main objective of the examination is to screen hidden abnormalities of the heart, abdomen and hips and reassure parents about the minor abnormalities and normal variants. Mother should always be at the bedside, so that she is allowed to express her concern. As soon as the baby is delivered baby should be taken in prewarmed baby tray. Cord is clamped and cut. Baby should never be kept naked for more than 1 minute.

Once the respiratory status of the child is settled, then the routine examination of the child is designed to assess the general status of health and to detect the hidden congenital anomalies.

Much of the time is devoted to inspection of the child. It includes awareness and activity of the child. Peripheral cyanosis is normal in newborn, but central cyanosis will indicate cardiac or respiratory disease. Cyanosis in the mucous membrane is more reliable in dark neonate. Presence of jaundice in first 24 hours is pathological and should be investigated.

Vernix caseosa, a greasy cheese-like material which disappears after few hours is present at the folds of the neck and groin. Newborn will have extremely smooth skin. Thin gelatinous skin is seen in preterm babies. Dry and cracked skin which tend to peel are seen in postmature child. Abnormally high pitched cry indicates CNS insult. Weak and feeble cry should be investigated.

Next anthropometric measurement of the neonate should be done. These include length, weight, head circumference, chest circumference, and upper segment and lower segment ratio. The vital parameters indicate status of the neonate. The normal ranges are given in **Box 3**.

After glancing through the inspectory findings and recording the vital parameters, any clues regarding congenital anomalies in the baby should be looked for. History suggestive of the amount of the amniotic fluid should be ascertained. Polyhydramnios in the mother is associated with upper intestinal obstruction like esophageal atresia and duodenal atresia. Oligohydramnios is associated with bilateral renal agenesis and obstructive uropathy.

Incidence of congenital anomalies are common among preterm babies. Usually one congenital anomaly will be associated with other congenital anomalies. Hypoplastic type of small-for-the-date babies are prone to have congenital anomalies.

Single umbilical artery is usually associated with imperforate anus, genitourinary abnormalities and esophageal atresia. Asymmetry of the face occurs as a result of congenital hypoplasia of depressor anguli oris muscle. Single palmar crease is seen in Down's syndrome. Potency of all the orifices and midline abnormalities should be seen.

Heart should be examined when the child is calm. Some systolic murmurs are common during first 48 hours. Breath sounds are equal and clear on both the sides. Faint crepitations heard are due to retained lung fluids. This will be absorbed spontaneously. Coarse crepitations are due to loose secretion in the upper airway and throat.

## REGIONAL PHYSICAL EXAMINATION

### Head

The shape and symmetry of the newborn vary considerably. Many factors are responsible for these variabilities. These include intrauterine position and pressure, presentation at the time of the delivery and the amount of molding during labor and delivery. The shape returns to normal within 3 days.

Babies born by vertex vaginal delivery will have some overriding or overlapping of the sutures. Caput succedaneum (**Figs. 1A and B**) and cephalohematoma (**Fig. 2**) may be encountered. One should be able to feel all the sutures in the baby's head. Sutural separation should also be examined. Normally sutural separation will not be more than 0.5 cm. Plagiocephaly is due to the flattening of the occiput and opposite frontal region. Head is lengthened in mentovertical axis with vertex and fronto-occipital axis in breech presentation.

The head shape is influenced by their presentation in utero. After vertex presentation and vaginal delivery, infants demonstrate pronounced vertical elongation of the head referred to as molding. Breech infants often have occipital-frontal head elongation, with a prominent occipital shelf.

The cranial sutures should be palpably open and may be separated by up to several millimeters at birth. Temporary overlap of bones, due to molding, should be distinguished from craniosynostosis (premature closure of a suture). If a suture closes in utero, it prevents growth of the skull perpendicular to the fused suture line, resulting in a sustained, abnormal skull configuration. In contrast, after molding occurs, the bones return to their normal positions in a few days, sometimes with a small concomitant decrease in head circumference.

Fontanelle is the depression between the skull bones and is covered by connective tissue. The gap may disappear if there is overlapping of bones due to molding. This should be differentiated from the craniosynostosis. There will be ridges in craniosynostosis. Usually there are size fontanelle at birth.

### BOX 3: Normal vital data of newborn.

Core temperature	–	36.5–37°C
Respiratory rate	–	40 per minute
Heart rate	–	120–140 per minute
Blood pressure	–	60/40 mm Hg

Anterior fontanelle is flat or concave when the baby is held in upright position and when the child is quiet. The size of the anterior fontanelle usually admits tip of the finger. It varies from 3–4 cm and closes by 18 months. It is sometimes pulsatile.

The posterior fontanelle measures about 0.5–4 cm and closes by 3–4 months. Encephalocele and depressed fracture are rare findings.

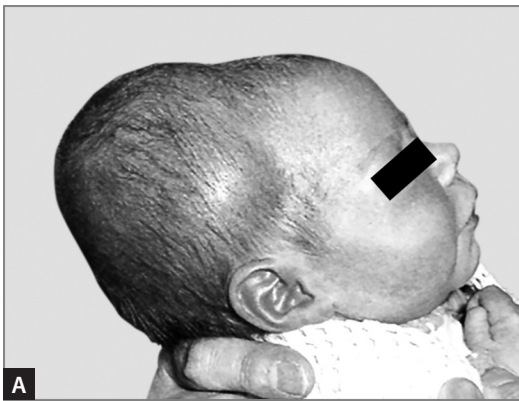
Transillumination of the head is performed as a screening test in the baby with an unusually large and asymmetrically shaped head. This is done before performing more accurate forms of intracranial diagnosis.

Transillumination test will be positive, when there is increased amount of fluid in subarachnoid, subdural or ventricular space. The condition includes severe hydrocephalus, chronic subdural hematoma or effusion and hydranencephaly. A bulging or tense fontanelle, with separation of

the bony sutures, indicates increased intracranial pressure. A circular hematoma may be seen at the site of application of a vacuum extractor.

## Face

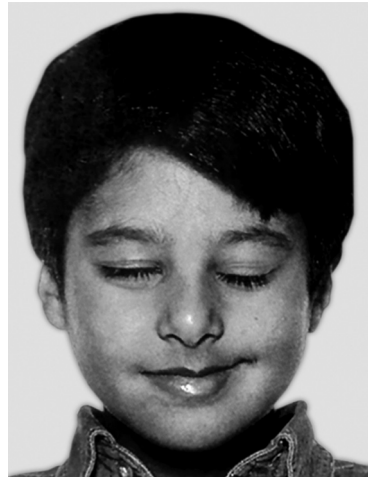
The newborn's face may indicate the presence of a dysmorphic syndrome. There may be obvious malformations, such as cleft lip or a small mandible (micrognathia). Intrauterine position may cause asymmetry of the face. Pressure over the stylomastoid foramen during labor may cause a peripheral facial paralysis, which is obvious during crying. The paralysis usually resolves and should be distinguished from congenital absence of the depressor anguli oris muscle, which also results in an asymmetric crying facies (**Fig. 3**). Fracture of the zygomatic arch can occur and is detectable by palpation. Forceps often leave bruises on the face usually in the shape of the forceps blade.



**Figs. 1A and B:** Caput succedaneum.



**Fig. 2:** Cephalohematoma.



**Fig. 3:** Bells palsy.

## Eyes

Newborns generally open their eyes when they are awake, held upright, and shaded from bright light. An infant who is quiet and alert will fix on the examiner's face and follow it.

The normal appearance of eye should be established. Eyelids are usually puffy and swollen at the time of birth. Eye should never be attempted to open. This maneuver will be many a times unsuccessful. The main ingredient in success is patience. If the baby is in quiet, alert state, it may open its eye spontaneously. Then baby may fix gaze on examiner. Baby will follow the examiner through an area of at least 90°. This along with presence of bilateral red reflex gives good first line assurance about baby's vision. Babies open their eyes when they are being fed. Eye movements are not fully coordinated at birth. Babies may have strabismus because of conjugate movement of the eyes in the young infants. This is only intermittent. Fundoscopy is not done routinely in newborn. This is limited to those in whom there is specific concern of the eyes. Such as prematurity, congenital infections, like rubella or cytomegalovirus.

It is mandatory to look at the pupil through the fundoscope from a distance to see the red reflex. This is done by looking straight on to the pupil from a few feet away. Bright red and orange glow of the pupils is the reflection of the light from the back of the retina. In congenital cataract, pupil will appear dull gray rather than bright orange.

Ophthalmoscopic examination should be performed in newborn infants prior to their discharge. One holds the ophthalmoscope close to the examiner's eye with the lens power set at 0. In a dark room, light is allowed to project simultaneously in both eyes and then individually from 18 inches away. It should begin by focusing on the anterior portion of the eye and then progressing back to the retina. This allows detection of anterior lesions, such as cataracts and colobomas of the iris. In fair babies, a red reflex is transmitted back through the lens, whereas in darker skinned infants a paler orange-tan color may be seen. It should be symmetrical in color and intensity. Visualizing retinal vessels verifies focusing on the retina. A diminished or absent red reflex suggests a cataract or other opacities. A white pupillary reflex is abnormal and may occur with a large retinoblastoma or developmental abnormalities such as retinal coloboma, retinopathy of prematurity, and persistent hypoplastic primary vitreous.

Birth trauma may cause subconjunctival hemorrhages or hemorrhages in the anterior chamber, vitreous, and retina. Forceps deliveries can result in lacerations of the lid or globe. A rupture of the Descemet membrane in the cornea may result in corneal clouding.

## Ears

At term, the ears are well-formed and contain sufficient cartilage to retain a normal shape and resist deformation. Gently pulling the pinna back and down aids examination of the ear canal and tympanic membrane. An alert, normal newborn will turn toward human speech and startle to a loud noise, which is a considered a crude estimate of hearing.

## Nose

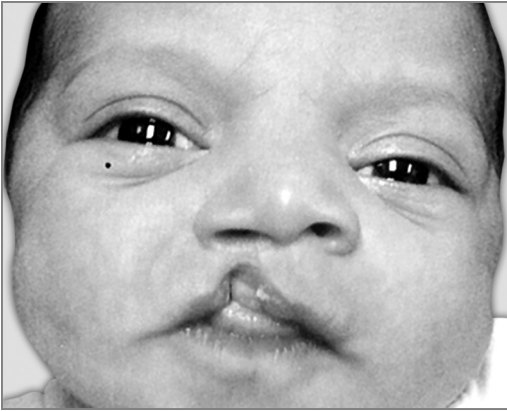
The main aim of examining nose is to assess the patency of both nares. Patency can be established by blocking one nostril and then the other with finger while the baby's mouth is closed. Air movements in each nostril is heard either directly or by stethoscope. Nasal stuffiness can occur as a result of retained mucus or trauma but could also suggest drug withdrawal.

In a suspected case of choanal atresia or stenosis, a soft catheter is passed through the passage. A baby with bilateral choanal atresia usually presents with respiratory distress and cyanosis. Distress and cyanosis will be relieved when baby opens the mouth or while crying.

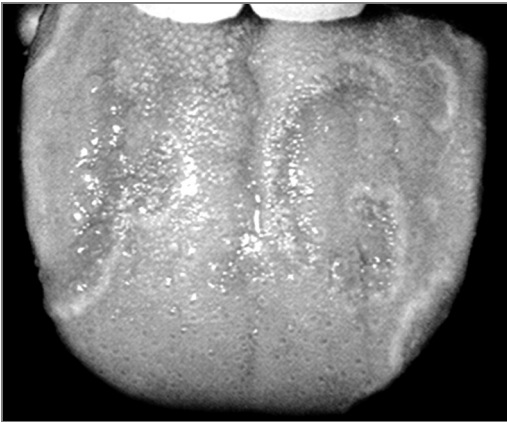
## Mouth

Examination of the mouth includes inspection and palpation. A cleft lip (**Fig. 4**) is seen on inspection, whereas cleft palate may not be seen but may be detectable by palpation; a cleft uvula should raise suspicion of a palatal defect. Small, shiny white masses on the gums (epithelial pearls) are common. White Epstein pearls are found in the midline on the roof of the mouth, at the junction of the hard and soft palate. A ranula is a small benign mass (i.e., mucocele) that arises from the floor of the mouth. A high-arched or narrow palate is found in many dysmorphic syndromes.

The tongue (**Fig. 5**) may be attached to a short central frenulum (i.e., ankyloglossia). An enlarged or protruding tongue can be seen with hemangiomas, isolated macroglossia, hypothyroidism, or in Down and Beckwith syndromes. The normal, awake newborn will usually suck vigorously on a finger placed in the mouth.



**Fig. 4:** Cleft lip.



**Fig. 5:** Geographic tongue.  
(For color version see Plate 5)

Natal teeth, if present, usually erupt in the lower incisor position. These can either be supernumerary teeth or true, deciduous milk teeth. If very loose or the cause of painful breastfeeding they may be removed.

Some newborns will have some mucus or saliva drooling from their mouth in the first few hours of the birth. This occurs as a result of swallowing of amniotic fluid and regurgitating the stomach contents.

Bluish retention cyst is present on the floor of the mouth. Sucking blisters are found at lips. Glossoptosis is the potential cause of airway obstruction.

## Neck

The neck of the newborn should have a full range of motion; limitation may indicate an abnormality of the cervical spine. Cervical masses, such as a

goiter, cavernous hemangioma, or cystic hygroma (**Figs. 6A and B**), may compress the trachea and cause inspiratory obstruction. Brachial cleft anomalies (**Fig. 6C**) include cysts or sinuses along the anterior edge of the sternocleidomastoid muscle (**Fig. 6D**). Thyroglossal duct cysts (**Figs. 7A and B**) usually occur in the ventral midline. Torticollis is seen with a tightened sternocleidomastoid muscle on one side and an atretic sternocleidomastoid muscle on the side toward which the head is turned; facial asymmetry is a common accompaniment.

Lateral traction during delivery may damage the upper root of the brachial plexus (C5 or C6 vertebra), resulting in paralysis of the shoulder and arm. The arm is held alongside the body in internal rotation, i.e., Duchenne-Erb paralysis) (**Figs. 8A and B**). The lower root of the brachial plexus (C8 or T1 vertebra) may be damaged, particularly during breech delivery. When this occurs, the small muscles of the hand are paralyzed, resulting in the absence of grasp reflex (i.e., Klumpke paralysis). When there is neck trauma, the cervical sympathetic nerves may be damaged, i.e., Horner syndrome), and the phrenic nerve may be injured, causing diaphragmatic paralysis.

Neck will be usually short in the newborn, fibroma of the sternocleidomastoid muscle, thyroglossal cyst, dermoid cyst and cystic hygroma are differential diagnoses of swelling of the neck.

Thyroid areas should be examined thoroughly to rule out thyroid swelling, especially if the mother is taking iodides during pregnancy or if there is family history of the thyroid disease.

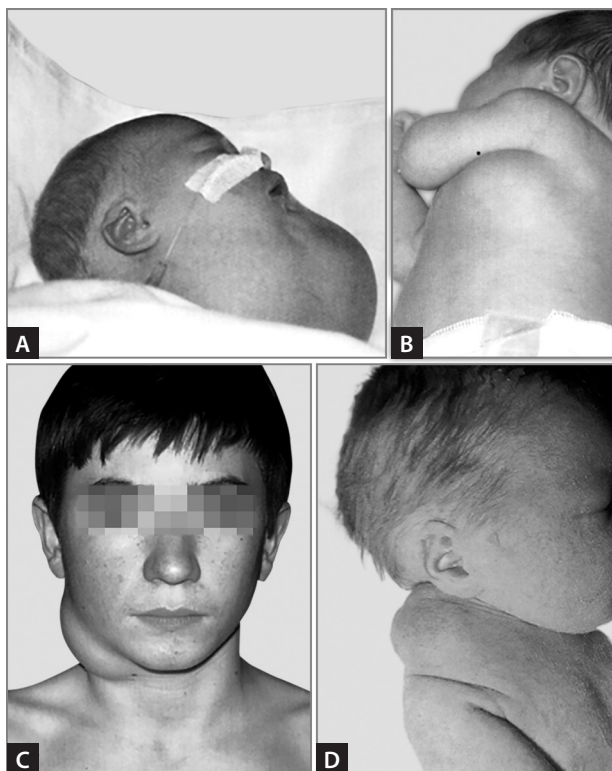
*Palpation of the clavicle:* The clavicle is the most commonly fractured bone during delivery. Palpation may reveal crepitus in the first few days. Soon after, a sizeable lump of the callus forms at the fracture site. It will gradually disappear completely over many months.

## Chest

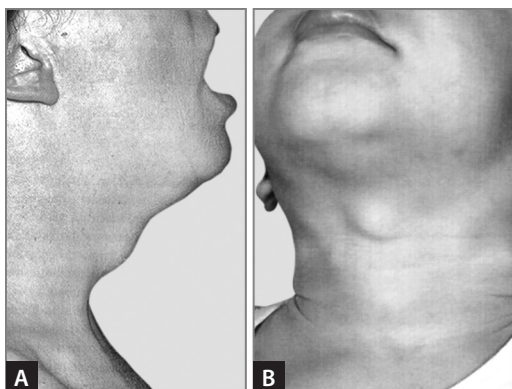
Any chest wall deformities like funnel chest or pigeon chest and presence of prominent xiphisternum is noted. Position, contour and form of the nipple or presence of accessory nipple should be looked for. Enlargement of the breast (**Fig. 9**) may occur in both male and female infants during 3rd and 4th week. Newborn may secrete milk from the nipple.

Ribs are more horizontal with increasing anteroposterior diameter of the chest. This limits the movements of the thoracic cage, the descent of the diaphragm, the abdominal contents and pushes the abdominal wall forward.

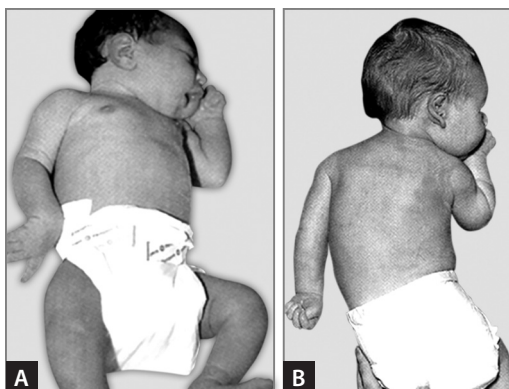




**Figs. 6A to D:** (A) Cystic hygroma; (B) Cystic hygroma; (C) Branchial cyst; (D) Sternocleidomastoid muscle tumor.  
(For color version (Fig. D) see Plate 5)



**Figs. 7A and B:** (A) Thyroglossal cyst on elevation;  
(B) Thyroglossal cyst.



**Figs. 8A and B:** Erb's palsy.

In newborn, respiration is normally irregular in both amplitude and frequency. This is associated with the pauses lasting less than 10 seconds. Irregular breathing pattern is more marked in pretermatures. The respiratory rate averages 30–40 breaths per minute, in a resting full-term baby. Breath sounds should be heard well in the front and the back, few crackles may be heard immediately after the birth within few hours.

Intercoastal retractions are normal during the first few minutes after birth. Thereafter, they are usually a sign of increased inspiratory effort from noncompliant lungs or airway obstruction. Mild expiratory grunting, nasal flaring, and tachypnea occur during the first few minutes after birth. Scattered crackles caused by residual retained intra-alveolar lung fluid often clears rapidly. Intercoastal indrawing is very common among

the preterm babies because of the softness of the ribs.

Overinflated chest is seen in meconium aspirated newborn.

When the airway is obstructed or the lungs are stiff, the abdomen appears to enlarge and the chest cage appears to get smaller with inspiration (i.e., thoracoabdominal asynchrony). Persistence or worsening of respiratory symptoms may indicate more serious problems.

## Cardiovascular System

The point of maximal cardiac impulse is at the fourth to fifth intercostal space and medial to the midclavicular line on the left side of the chest. This may be displaced if there is a pneumothorax or space-occupying lesion.

The heart rate may be 160–180 beats per minute (bpm) during the first few hours after birth. Thereafter, the normal awake heart rate averages 120–130 bpm. Occasionally, a normal newborn infant may have a heart rate of 80 bpm, which may fall transiently to 60 bpm for short periods.

It will vary when the child is crying and taking feeds. Occasional extra systoles are common. The two heart sounds are usually equal in intensity. The normal variation of the width of the split in the second sound with the respiration may be difficult to appreciate because the respiratory or heart rate is rapid.

Despite the rapid heart rate, heart sounds can be clearly distinguished. The pulmonic component of second sound, may be prominent on the 1st day. Splitting of the second sound is audible along the left upper and midsternum. While postnatal circulatory adjustments are occurring,

transient benign murmurs can be heard over the pulmonic area or cardiac apex. Murmurs, other physical signs such as cyanosis, poor perfusion, tachypnea, difficulty in palpating pulses or brachiofemoral delay require further evaluation.

Sometimes, in the first few days, it is common to hear soft precordial systolic murmurs. This is probably due to flow through ductus arteriosus, that remain patent immediately after the birth. This closes gradually over the hours or days. Cardiac murmur heard during first 48 hours can be transient or a significant murmur.

*Criteria for significant murmur:*

- Loud grade III murmur—abnormal second heart sound
- Associated ejection click

Cyanosis in neonate indicates hypoxemia. It is due to shunting of the venous blood from pulmonary to systemic circulation, i.e., right to left shunt.

Radial and femoral pulses should be palpated and compared to the other side. Absence of femoral pulse, brachiofemoral delay indicates the coarctation of aorta.

## Abdomen

Infants often have abdomens that are bulging at the sides but they should be soft. History of maternal polyhydramnios should raise concern for the possible intestinal obstruction. A gap between the abdominal rectus muscles in the midline (i.e., diastasis recti) (**Fig. 10**), most noticeable with crying 15 quite common. There is also often a small defect in the periumbilical musculature of the anterior abdominal wall, which may allow an



**Fig. 9:** Breast engorgement—newborn.



**Fig. 10:** Diastasis recti.



**Fig. 11:** Umbilical granuloma.  
(For color version see Plate 5)



**Fig. 12:** Umbilical hernia.

umbilical hernia; this usually closes as the muscles develop toward the end of the 1st year.

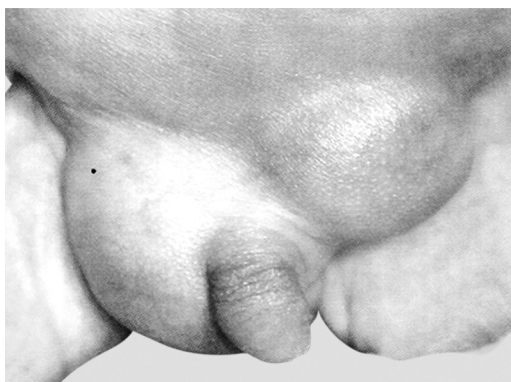
Umbilical cord should be inspected for number of vessels present in it. Shrinkage of the cord with the drying occurs rapidly after the birth as a result of closure of umbilical arteries. This produces deprivation of the blood supply to tissues.

The umbilical cord normally contains two arteries and one vein, with the vein being larger than the arteries. Approximately 1% of newborns have a single umbilical artery, and 15% of these have one or more congenital anomalies, usually involving the nervous, gastrointestinal, genitourinary, pulmonary, or cardiovascular system.

The umbilical cord usually falls off between 10 and 14 days, releasing a small amount of opaque, yellowish discharge. Delayed separation of the cord, past 3 weeks, often occurs in infants with defective phagocyte function. Application of local antiseptics prevents the delay in separation. A discharge from the cord stump should exclude infant with persistent urachus. Umbilical granuloma (**Fig. 11**) is a firm tissue present at the site of separation. This has to be distinguished from the polyp in the persistent part of mesenteric duct. This requires surgical removal. Cord granuloma can be treated with copper sulfate granule application.

In intrauterine growth retarded baby, the cord is often thin and stingy with little Wharton's jelly. In baby who has been bathed in meconium in utero for more than few hours, the cord may be stained green.

Umbilical hernia (**Fig. 12**) may be present at birth. It is more common among preterm and low birth weight babies. Gastroschisis or omphalocele can occur due to diversification of recti. Hernias (**Fig. 13**) are commonly seen in preterm newborn.



**Fig. 13:** Bilateral inguinal hernia.

Palpation of the abdomen is simple during the feed, but care must be taken not to cause vomiting.

## Liver

Normally liver is palpable in epigastrium. Poorly defined liver edge is palpable in the right upper quadrant by applying the thumb or fingers gently to the surface of the skin. The edge is normally felt 1–2 cm below the right costal margin in the midaxillary line.

## Spleen

Spleen may or may not be palpable in newborn. It is enlarged more laterally than in the older children. Tip points to the left rather than the right loin. Ability to palpate the tip of the spleen on deep inspiration is not always an indication of abnormality. But this should be considered along with other findings. Palpation should also include a search for unusual masses.

## Kidneys

Renal examination is easiest on the 1st day, before the bowel is filled with gas. The lower portion of each kidney is normally palpable on each side; the lateral and lower edges can be felt above the level of the umbilicus and lateral to the midclavicular line. During the 3rd day, only the lower pole is palpable. The right kidney is situated slightly lower than the left kidney, and the palpable portion of the kidney normally feels about 2 cm wide. Unless they are enlarged and abdomen is unusually soft, bladder is usually palpable in infancy.

## Anus

A thorough examination is required to confirm anal patency, as an imperforate anus is not always obvious on inspection. A normal appearing anal dimple can exist with no opening. A fistula that opens onto the perineum, ventral to the normal anus, may also accompany the imperforate anus. However, this fistula will not have the radiating skin creases of a normal anus. Presence of meconium on the perineum and perianal area does not rule out imperforate anus; meconium in the anal area may have been passed by way of the skin fistula or, in a girl, a fistula from the rectum to the vagina. Rectal prolapse (**Fig. 14**) in which rectum starts to push through the anus. This is seen malnutrition and whooping cough.

## Genitalia

Genitalia examination will help to estimate the gestational age. In male glans penis is normally covered completely by prepuce that should not be fully retracted. Penile foreskin is adherent. Normally, urine should pass in full stream without ballooning the prepuce.

Identification of the urethral opening is important. Hooded prepuce is present with hypospadias.

Scrotum is best examined with the quiet baby and warm hand. Scrotum is usually large as it is the embryonic analogue of the tibia of female. Scrotum in a full-term boy is pendulous and rugosity is well formed. It may be more pigmented than the rest of the skin.

Both the gonads should be palpable and capable of being brought into the scrotum. The testes should be completely descended. The normal testis is 1–2 cm long and should be identical in size, neither soft nor hard in consistency.

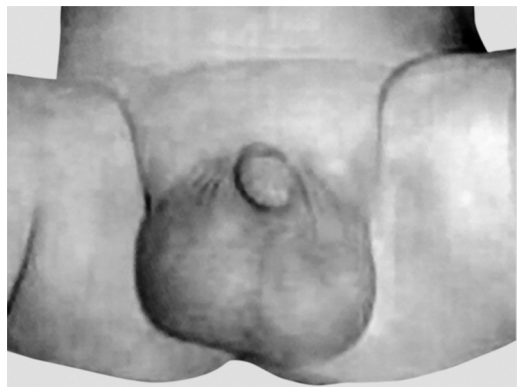
Hydrocele (**Fig. 15**) of the tunica vaginalis. Small collection of fluid disappear within few days if it is communicating type. Large collection of fluid around the cord should lead to hernia.

In preterm female infants, separation of the labia majora may give the illusion that the clitoris is enlarged. In term female infants, the labia majora meet in the midline, covering the rest of the genitalia. It is important to identify the urethra, which is just below the clitoris, and the vagina as distinct orifices; a single orifice or urogenital sinus is abnormal.

In female newborn, genitalia will have relatively large labia majora, that cover and occlude the labia minora and vaginal introitus. Considerable thick vaginal discharge may be present, especially on the 2nd and 3rd day. Minor bleeding is also noted. This is normal unless there is more blood loss in the urine. Mucosal tag from wall of the vagina is seen. These are common abnormalities. In girls, clitoris is prominent. If the infant is premature labia minora is also seen covered by labia majora. In case of ambiguous genitalia, a chromosomal analysis should be done.



**Fig. 14:** Rectal prolapse.  
(For color version see Plate 6)



**Fig. 15:** Congenital hydrocele.



Ambiguous genitalia is a term that encompasses a wide range of findings such as enlargement of the clitoris and varying degrees of labial fusion in females or micropenis, hypospadias with bifid scrotum, and cryptorchidism in males. As the distinction between a male and female can often be difficult, the assistance of a pediatric endocrinologist is warranted. In such situations, it may be prudent to avoid assigning a sex until further investigation.

## Extremities

Upper limb abnormalities of the hand are common features of dysmorphism. Number of the fingers and toes, presence of syndactyly should be looked and noted slight syndactyly of the second and third toes is a common minor congenital anomaly.

Traumatic injuries to the limbs can occur as a consequence of intrauterine positioning and delivery. These include fractures in the shaft of the femur, humerus, or clavicles and injury to the brachial plexus, causing paralysis of the hand and arm.

It is important to be able to distinguish normal variations in joint positions from joints that are deformed. As a rule, if simple manual pressure will correct a deformed joint back to its neutral position, then corrective positioning or simple exercise and stretching will correct the deformity. If the deformity cannot be corrected by gentle pressure, orthopedic evaluation is needed.

With the hips flexed to 90°, the legs normally can be abducted until the knees touch the table the infant is lying on. If this cannot be done, there may be developmental dysplasia of the hip. Female infants constrained in a breech position in utero are at a higher risk. In this condition, the head of the femur is displaced posteriorly,

out of the acetabular fossa. The affected leg may appear shorter. The examiner will feel a click when abducting and adducting the hips in about 10% of all infants. However, only 10% of infants with hip clicks have developmental dysplasia of the hip. The Ortolani and the Barlow maneuvers can test for a dislocatable hip.

Malformations of the limbs are often obvious (**Figs. 16A and B**). Often, limb abnormalities are indicators of underlying genetic syndromes. The notable exceptions are those associated with traumatic amputation from amniotic band syndrome. These intrauterine constriction bands may amputate the digits or cause localized edema by obstructing lymphatic drainage.

Rudimentary skin tags at the lateral border of either fifth finger or toe may represent rudimentary supernumerary digits. Extra-long nails are common in post-term infants.

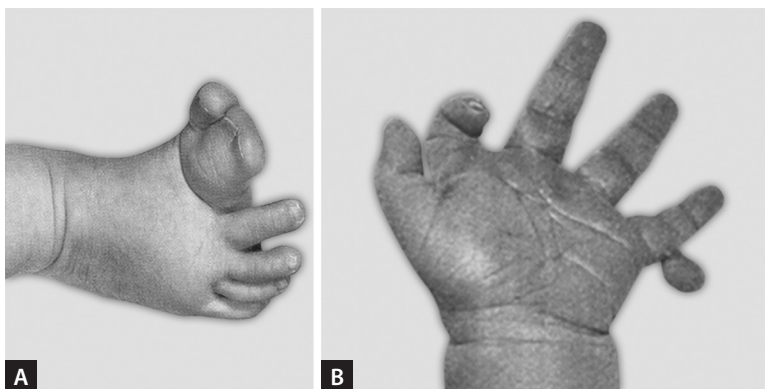
Most normal newborns have slight bowing of legs. This disappears gradually as the child gets older. This reflects intrauterine position.

Postural talipes should be differentiated from true talipes. Postural type can always be straightened. It usually reverts to normal within few weeks.

## Back

### Spine

The spine of the newborn is quite flexible in both the dorsoventral and lateral axes; restricted movement suggests vertebral anomalies. The entire length of the spine, including the sacrum, should be palpated for bony defects and asymmetries. A midline abnormality of the skin over the spine, such as a small dimple, tufts of hair, or a pilonidal sinus, may indicate an occult spina bifida, or a diastematomyelia (i.e., a division of



**Figs. 16A and B:** (A) Polydactyly and syndactyly; (B) Extra digits.



the spinal cord into two parts, which may become tethered as the child grows). Neural tube defects (i.e., meningocele and myelomeningocele) and tumors of the spine (i.e., teratomas) also may be present at birth.

Back is completely examined till down the natal cleft. Congenital defects in the dorsal surface may give clue for internal anomalies. Pilonidal sinus is the common finding present. This may disappear gradually and has no special significance.

Any hemangioma, lipoma or tuft of hair that crosses the midline of the lower back has high probability of internal structural spinal abnormalities.

Neural tube defects may be small but they are always on the midline. It is the common site for stroke bite, midline hairy nevus, spina bifida. Any fixed deformity should be ruled out such as kyphosis and scoliosis. Sacrococcygeal teratoma is seen immediately posterior to anus. Four percent of them are malignant.

Truncal tone is assessed by supporting the baby with left hand. The right hand is used to steady the back. In case of floppy baby, child remains like rag-doll. Spine and limbs are normally flexed, but there may be momentary extension of neck. This is called ventral suspension.

## Nervous System

Interpretation of neurologic signs in a newborn infant requires knowledge of normal development because maturational changes parallel increase in level and complexity of neurologic function. It is useful to retain the basic approach in evaluating neurologic function, including a systematic assessment of mental status (i.e., level of alertness), cranial nerve function, the motor and sensory systems, and the evoked reflexes.

Nervous system starts with the sensorium of the child. It is otherwise, the alertness of the child. It is classified as.

State of wakefulness in neonate:

- State I – Deep sleep with regular respiration
- State II – Light sleep with regular respiration
- State III – Eyes open with no gross body movements
- State IV – Eyes open with gross body movements
- State V – Eyes open or closed and crying

## BEHAVIOR OF THE NEWBORN INFANT

Mental status examination consists of observing spontaneous eye opening and movements of the

eyes, face, and extremities, as well as the response to stimulation. A preterm infant born before 32 weeks of gestation spends much of the time sleeping but can be aroused by gentle stimulation. After 32 weeks of gestation, there are periods of spontaneous eye opening with roving eye movements and movements of the face and extremities. The irritable and agitated infant cries spontaneously with minimal stimulation and cannot be calmed. Delayed or poorly maintained response to stimulation: suggests, lethargy in coma, arousal is impossible.

It is determined by internal resources and the response to external environment. Infant's behavior can be judged at rest after stimulation. The mother and child can start with positive attitude.

## Motor Functions

The motor examination assesses spontaneous movements and muscle tone. Posture and resistance of muscles to passive movement evaluate passive tone. Evoked changes in extremity tone and evoked postures of the head, trunk, and extremities assess active tone.

## Tendon Reflexes

In the term infant, biceps, knee, and ankle jerks can be elicited readily, and ankle clonus is also common. Asymmetry or absence of reflexes may indicate a significant central or peripheral nervous system abnormality. Eliciting a plantar response is of limited value.

Spontaneous movements normally take place when the baby is awake consisting of alternating flexion and extension. Normally the tone of the newborn is hypertonía and that of preterm is hypotonia. Deep tendon reflexes are usually brisk and variable. Normally ankle clonus may be present with 6–8 jerks uninterrupted.

## Examination of the Cranial Nerve

First cranial nerve cannot be tested in the newborn or neonate. Second cranial nerve can be examined by the way the child turns to diffuse light. If both the eyes rotate in the same direction, it suggests that the III, IV, VI cranial nerves are intact. Doll's eyes response in turning of the eye in the opposite direction involves the integrity of III, IV and VI cranial nerves. Ptosis (**Fig. 17**) and pupillary reaction signify II and cranial nerve.

Presence of the rooting reflex indicates that Vth nerve is intact and crying and grimace suggest the VIIth cranial nerve.



**Fig. 17:** Ptosis of left upper lid.

Optokinetic nystagmus is elicited by holding the baby on the back on outstretched arms, hands supporting the occiput and gently turning slowly in clockwise direction. This suggests the intact vestibular part of the VIIIth nerve. Startle response indicates auditory part of the VIIIth nerve. IX and Xth cranial nerves are judged by gag reflex. Vigorous sucking and stripping action by tongue suggests that XIIth cranial nerve is intact.

During the last trimester of gestation, changes occur in tone and primitive reflexes. Flexor tone increases in the lower extremities and progresses cephalad between 28 and 40 weeks of gestation. After 40 weeks of gestation, maturation of tone and coordination begins rostrally and progresses caudally. For example, the infant at 28 weeks of gestation lies with both upper and lower extremities fully extended with little or no resistance to passive movement of the extremities. As the infant matures, by 34 weeks, the lower extremities are flexed, and by 36 weeks, the upper extremities are flexed. Term infants demonstrate flexion in both upper and lower extremities. At term, both neck flexors and extensors can maintain the head in the axis of the trunk for more than a few seconds.

### Involuntary Movements

The frequency and symmetry of spontaneous movements vary with the infant's level of arousal; normal spontaneous movements of the extremities in the term infant are organized and smooth. The ability to abduct the thumb is particularly meaningful, as persistent adduction suggests a corticospinal tract lesion. Jitteriness and seizures are involuntary movements that require further evaluation. Jitteriness consists of tremor-like movements of extremities that are very sensitive to stimuli and can be stopped with gentle passive

flexion. Jitteriness may be found in hypoglycemia, hypocalcemia, and hypoxic ischemic encephalopathy, but often no specific cause is identified. Seizures are difficult to diagnose clinically and suspicion requires confirmation with electroencephalography. Many infants demonstrate myoclonic jerks during the onset of sleep that are mistaken for seizures.

### Posture and Passive Tone

The symmetry and maturity of passive tone are evaluated by observing the resting posture of the infant and by moving the extremities while the infant is awake and quiet. The degree of resistance to slow, gentle movement of the extremities and extremity angles ascertain passive tone. The infant's head must be in the midline position during the motor examination to avoid eliciting asymmetries in tone provoked by the asymmetric tonic neck reflex. In a normal baby, flexion always exceeds extension.

### Active Tone and Primitive Reflexes

Active tone refers to the infant's tone during active movement in reaction to certain situations. Active tone and evoked reflexes are evaluated by observing changes in the infant's posture in response to changes in position with respect to gravity or by observing the infant's responses to other stimuli, such as touch and pressure. Of the many primitive reflexes described in neonates, only a few, including the righting reaction and raise-to-sit maneuver are routinely assessed. These are normally present in term and preterm infants and do not disappear until the infant reaches several months of age. Absence of primitive reflexes in the newborn infant indicates central nervous system depression.

### Maturation Changes in Tone and Reflexes

Maternal menstrual history or early fetal sonography provide the best possible dating before 32 weeks of gestation; from 32 weeks on, it appears reasonable to confirm gestational age by physical criteria and central nervous system function of the infant according to the normal steps of development. In this assessment, structured evaluation of passive tone, active tone, and primary reflexes are used to determine gestational age within 2-week periods. A definite conclusion on neurologic maturation is reached only if 7 of the 10 responses correspond to the same 2-week gestation period. When more than three responses are out of line,

no firm conclusion can be made. Such a result also raises the probability of a neurologic abnormality.

## Sensory Examination

Sensory function has limited value in newborn. Anal reflex should be tested in neural tube defects. Vision is very difficult to test. It is told that visual acuity in newborn is 6/45.

Hearing is judged by startle response including blinking of the eye and changes in the heart rate. These changes are seen as response to 500–1000 cycles per second.

## Hip Joint Examination

### *Stability of the Joint*

The most common screening maneuver combines those described by Ortolani and Barlow. With the baby supine on a firm surface, flex its thighs to right angle to the abdomen and its knees to the right angle to thighs. Then, the thigh is grasped with the examiner's fingers along the outside of the shaft of the femur, with the middle fingertips on the greater trochanter, and examiner's thumb medially in the femoral triangle.

With the baby at rest, first femur is adducted completely and gently abducted from the position of full adduction so that knees come to lie laterally on the mattress. During abduction, greater trochanter is pushed medially with the fingers. If there is a click either during adduction or abduction or if there is resistance as the knee approaches full abduction or if there is a spasm or discomfort of the abductor muscles of the femur, the baby probably has congenitally dislocated or dislocatable hip.

*Unstable hips*, many unstable joints, following breech delivery become stable within few days. It is prudent to re-examine the hips after 24–48 hours.

*Dislocated hips*: Here abduction at the affected hip is limited and difficulty in abducting either hip to 80° should arise the suspicion of congenital dislocation.

Pediatrician should be alerted, of some of the signs or symptoms listed in **Box 4** are noticed.

## Reflexes

*Grasp reflex*: This is elicited in hand and feet. This is done by pressing the finger lightly against the palm and sole. The lightness of the grasp in often sufficient. This is enough for traction response. It is generally safer to do this by holding the infant's wrist and pulling him slowly to the sitting posture.

### BOX 4: Alarming signs in neonate.

- Bleeding from any site
- Appearance of jaundice within 24 hours
- Poor feeding
- Lethargy
- Excessive crying
- Respiratory distress or cyanosis
- Convulsions
- Not passing urine within 72 hours
- Not passing motion within 24 hours

The infant flexes his elbows as if he is trying to assist the movements. Hence, attempt should be made to hold the head in line with the trunk as it is raised.

*Moro reflex*: This is elicited by allowing the head to fall back unsupported for a short distance. Sudden extension and abduction of the limbs followed by slower adduction and flexion to the resting position.

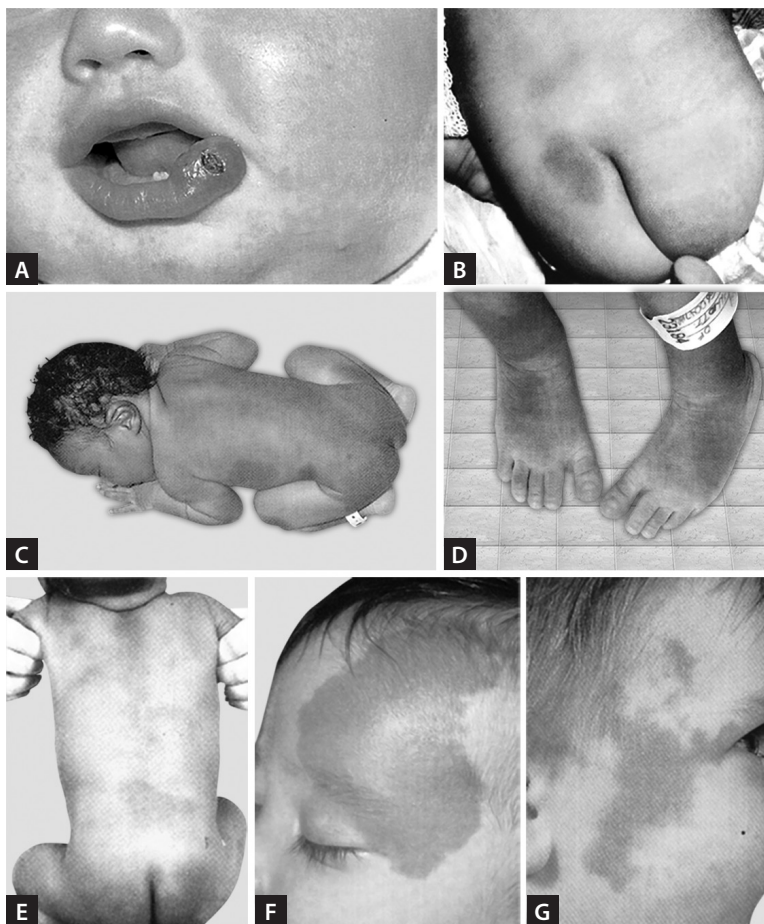
*Rooting reflex*: This is elicited by touching the infant's cheeks to turn eagerly to the side. This is stimulated in the hope of finding the nipple.

*Crossed extension response*: This is elicited by extending one leg and tickling the other sole. A positive response is movement of extension possibly with the adduction to the lower leg.

*Stepping movements*: When the child is held erect with the feet on a firm surface, a full-term infant attempts to straighten trunk and make a stepping movement with his legs.

## Skin of the Newborn (Figs. 18A to G)

Fine, soft, lanugo hair covers the entire body in very preterm infants and disappears from the face and lower back between 32 and 37 weeks. The term infant has lanugo hair on the upper back and dorsal aspects of the limbs. Vernix caseosa, a thick, white material with the consistency of soft cheese, covers the skin of the entire body until 35–37 weeks. By term, the amount of vernix is limited mainly to the flexor creases. The subcutaneous tissue is relatively thick, and the fingernails and toenails are fully formed and extend slightly beyond the ends of the digits. If fetal stress occurs at term, meconium may be passed into the amniotic fluid. If meconium has been in the amniotic fluid for several hours, it will also stain the skin, fingernails, toenails, and umbilical cord with fetuses at less than 34 weeks of gestation rarely pass meconium. The postmature infant (beyond 42 weeks) may have a somewhat wasted appearance with dry,



**Figs. 18A to G:** (A) Strawberry hemangioma; (B) Mongolian spots; (C to E) Mongolian blue spots; (F and G) Port-Wine stains.

(For color version see Plate 6)

peeling skin, a decreased amount of subcutaneous tissue, long fingernails, and an alert appearance.

**Skin abnormalities:** Neonates often have skin rashes, some of which indicate a serious systemic issue. Much more common than these serious rashes are many benign skin lesions that are important to recognize and explain to parents.

**Color:** There may be cyanosis of the hands and feet (acrocyanosis), which is normal immediately after birth or if the infant has been exposed to a cold environment. Harlequin skin describes a transient change in the skin color of no known pathologic significance: one side of the body turns pale while the other side remains pink with a sharp line of demarcation in the midline.

Ecchymoses or localized petechiae generally result from birth trauma and are often present

over the head after vertex delivery or on the feet, lower limbs, and buttocks following breech delivery. More generalized petechiae suggest thrombocytopenia—subcutaneous. Fat necrosis appears as red lesions where the subcutaneous tissue is hard and sharply demarcated, and is usually seen over the cheeks, buttocks, limbs, or back.

Neonatal jaundice is caused by an elevation in indirect-reacting bilirubin, resulting in a yellow-to-green discoloration of skin. It is assessed by briefly pressing on the infant's skin with a finger and observing the color in the blanched area. One must be cautious in interpreting the intensity of jaundice based on physical examination as visual assessment of jaundice has been shown to be unreliable. Mild physiologic jaundice usually develops 2–4 days after birth. However, jaundice in the 1st day warrants prompt investigation; it is



usually from sepsis or hemolytic anemia. Keloid (**Fig. 19**) is a raised scar caused by an excess of protein (collagen) in the skin during healing.

### Vernix Caseosa

At birth the normal full-term infant is covered by vernix caseosa. It is a greasy substance that protects the skin during the lengthy immersion in amniotic fluid. This is the normal sebaceous secretion of the skin. The skin of the face and head may exhibit a variety of changes. It is important to reassure the parents.

### Angiomatous Lesion (Figs. 18F and G, 20, 21)

These are small, flame-shaped, flat hemangioma over the eyelids and the roof of the nose. These should be differentiated from port-wine stains. These are larger, permanent and may involve areas of face or head in a particular nerve distribution, especially trigeminal nerve distribution.

### Milia

These are small white spots on the face. These represent hyperactive sebaceous glands with visible retained secretion.

### Petechiae

Petechiae on the face are quiet common. These are pinpoint in size. They do not blanch with pressure. They usually result from increased presence in the venous system during a vertex vaginal delivery. They may appear on the face on face presentation, on buttocks after breech delivery. Bruising, i.e., ecchymoses may be related to delivery trauma.

### Erythema Toxicum

It is a newborn rash which is extremely common in full-term infants. The lesions usually appear as white pustules on an erythematous base. These are 1–3 mm in diameter and occur singly or in groups. The lesions contain many eosinophils. In case of pustules, lesions contain gram-positive cocci like characteristic pustules.

The skin changes seen in postmaturity are dryness, flakiness or cracking of the skin. The skin lesions that should cause concern and warrant close observation, investigation and treatment often include vesicles, pustules, areas of absent skin either congenital or acquired large bulky subcutaneous hemangioma. Visceral larva migrans is caused by migratory larvae of certain nematodes



**Fig. 19:** Keloid.

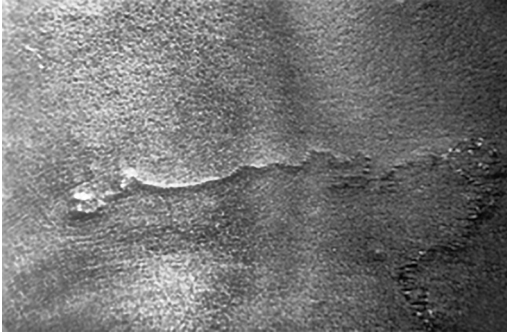


**Fig. 20:** Salmon patch.  
(For color version see Plate 6)



**Fig. 21:** Strawberry hemangioma.  
(For color version see Plate 6)





**Fig. 22:** Visceral larva migrans.  
(For color version see Plate 7)

such as *Toxocara canis*, *Toxocara cati*, and *Ascaris* (Fig. 22).

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# Premature Infant

## PRESENTING COMPLAINTS

A newborn child was brought with the complaints of:

- Preterm delivery of the newborn
- Low birth weight (LBW) baby

## History of Presenting Complaints

The newborn child delivered by emergency cesarean section was referred to the doctor in-charge of neonatal intensive care unit (NICU). The delivery was attended by the resident doctor working in pediatrics department. The mother was not registered case in antenatal health check-up. She was not aware of duration of the pregnancy.

One day she came with history of epigastric pain with swelling of the face and lower limbs. On examination, the blood pressure of the mother was recorded as 210/160 mm Hg. Her urine albumin was +++. These along with her clinical findings suggested that the mother was in imminent eclampsia. Hence, obstetrician decided to induce the delivery. As mother had first sibling being

delivered by cesarean section, the emergency cesarean section was planned. Before the section, emergency ultrasound examination showed approximate age of the fetus was 30 weeks.

Female baby cried immediately, after the delivery. The cry of the baby was good. Apgar score at 1 and 5 minutes were 8 and 10, respectively. The birth weight of the female baby was 1.1 kg. Hence, later the baby was shifted to NICU. This was the second sibling of nonconsanguineous marriage. First child was 2-year-old and maintains the good health.

## EXAMINATION

Girl baby was LBW. It was lying on the bed with increased tone. It used to respond to the tactile stimulus by crying. Signs of prematurity were present. Premature edema was present. Acrocyanosis was present. Features of intrauterine growth restriction (IUGR) were present. Labia were separated. Newborn was afebrile. The heart rate was 136 per minute and the respiratory rate was 42 per minute. The blood pressure recorded was 50/30 mm Hg.

The anthropometric measurements included, the weight was 1.1 kg (<3rd centile), the length of the child was 45 cm (<3rd centile), and the head circumference was 30 cm.

Respiratory system revealed presence of crepitation. Cardiovascular system showed first and second heart sounds were normal, and no evidence of congenital heart disease. Her abdomen examination was normal. No clinical evidence of congenital anomalies.

## INVESTIGATION

Hemoglobin	: 13 g/dL
TLC	: 10,500 cells/cu mm
DLC	: $P_{78} L_{20} E_2 M_0$
CRP	: Negative
Blood sugar	: 80 mg/dL
Serum calcium	: 8 mg/dL

### CASE AT A GLANCE

#### Basic Findings

Length	: 45 cm (<3rd centile)
Weight	: 1.1 kg (<3rd centile)
Temperature	: 37°C
Pulse rate	: 136 per minute
Respiratory rate	: 42 per minute
Blood pressure	: 50/30 mm Hg

#### Positive Findings

##### History

- Unbooked cases
- Maternal blood pressure
- Swelling of the face
- Epigastric pain

##### Examination

- Maternal hypertension
- Imminent eclampsia
- Low birth weight
- Respiratory system—crepitation
- Preterm baby

Blood group and  
Rh typing : AB positive  
Chest X-ray : NAD

## DISCUSSION

About 10–30% of all the birth are of LBW. Majority of them will be small for age, and 60% of the LBW babies are appropriate for the gestational age.

If the gestational age is less than 37 weeks, then it is called preterm or premature delivery. About 5% of the pregnancies are preterm delivery and 2% of them are before 32 weeks. These children are immature both anatomically and functionally.

## PROBLEMS OF PREMATURITY

The basic underlying feature of the LBW babies is immaturity of the organ system. These babies lack brown fat, which helps to keep themselves warm. Infants born before 34 weeks of gestational age will have uncoordinated neonatal reflexes.

### Respiratory System

These neonates will have poor alveolar diffusion of gases. This predisposes to resuscitation difficulties. Hence, these neonates present with respiratory distress syndrome (RDS) and apnea. These are associated with poor surfactant.

### Central Nervous System

Intraventricular hemorrhage (IVH) is more common because of delicate vessels. Immaturity of the system is manifested by inactivity, lethargy, poor cough reflex, uncoordinated sucking and swallowing reflexes. Blood-brain barrier is inefficient and hence the damage may occur at low-serum bilirubin levels.

### Cardiovascular System

The closure of ductus arteriosus is delayed. Hence, patent ductus arteriosus (PDA) may present with congestive cardiac failure (CCF). Hypovolemia will result with hypotension. Cardiac dysfunction will also occur.

### Gastrointestinal System

Regurgitation and aspiration are common because of uncoordinated sucking, small capacity of the stomach, incompetence of the cardioesophageal junction and poor cough reflex. Abdominal distension and functional obstruction are due to hypotonic.

## Infection

The low levels of immunoglobulin G (IgG) antibodies and inefficient cellular immunity predispose them to infections. Humid atmosphere, contaminated instrument will contribute to the incidence of infection.

## Metabolic Disorders

The poor hepatic glycogen stores, birth asphyxia and RDS contribute to the development of hypoglycemia. The blood urea nitrogen (BUN) is high due to low-glomerular filtration rate and acidosis develops early. These infants are prone to develop hypoglycemia, hypocalcemia and hypoxia. Electrolyte imbalance occurs due to immature kidneys.

## Blood Disorders

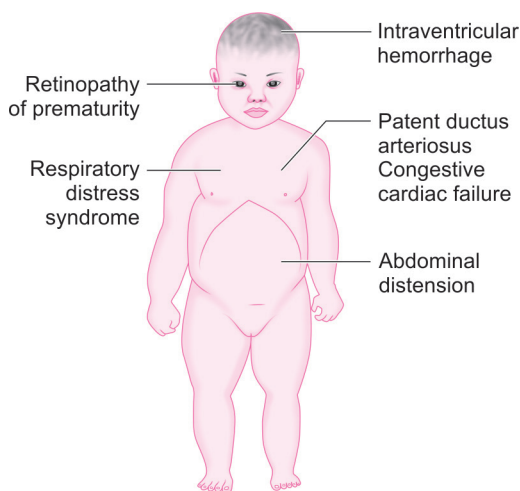
Premature infants are prone to develop hemolytic anemia, thrombocytopenia and edema at 6–10 weeks of age. Hyperbilirubinemia is also a feature.

## Eye

Retrolental fibroplasia due to oxygen toxicity is seen particularly in newborn with gestational age less than 35 weeks.

## CLINICAL FEATURES (FIG. 1)

- Thin red shiny skin, often covered with lanugo
- Lanugo are especially seen on back and shoulder
- Poor muscle tone, floppy and lie in frog-like posture



**Fig. 1:** Clinical features.

- Ears of little cartilage and very soft
- Genitalia are poorly developed
- Small scrotum with scaly rugosity
- Prominent labia minora and an enlarged clitoris
- Testes are present in external ring
- Breast nodule is with 5 mm thickness
- Single deep crease in anterior one-third of the sole

#### GENERAL FEATURES

- Immaturity of organ system
- Regurgitation and aspiration
- Infection
- Hypoglycemia
- Hypoxia
- Hypocalcemia
- Hemolytic anemia
- Thrombocytopenia

## PROBLEMS OF PREMATURE INFANT

### Early

- Hypoxia, apnea
- Respiratory distress syndrome
- Patent ductus arteriosus
- Septicemia
- Jaundice
- Periventricular bleeding
- Hypoglycemia, hypocalcemia, and hypothermia

### Late

- Septicemia, necrotizing enterocolitis (NEC)
- Bronchopulmonary dysplasia
- Anemia
- Cerebral palsy
- Jaundice
- Osteopenia of prematurity
- Retinopathy of prematurity (ROP)
- Growth impairment

## Neonatal Management

Immediate management include management of respiratory problem and stabilization of vital parameters. Adequate oxygen delivery and maintenance of proper temperature are the mainstay of management. Warm condition of the baby should be given prime importance as hypothermia can lead to hypoglycemia, bleeding diathesis, pulmonary hemorrhage, acidosis, apnea and respiratory failure. Adequate oxygenation is achieved by oxygen therapy and assisted ventilation. PDA requires conservative management with adequate

oxygenation, fluid restriction and diuretics. Indomethacin may be necessary. Skin leads to marked evaporation. Fluid loss particularly if baby is under radiant warmer in turn leads to hypernatremia. Alternatively immature kidney fails to conserve sodium resulting in hyponatremia.

The management of a patient with impending premature delivery should include the following: Evaluation of gestational age by dates and/or early ultrasound, fetal size and position, condition of the fetal membranes, amount of amniotic fluid volume, and evidence of chorioamnionitis and other obstetric complications such as bleeding, toxemia, etc.

For patients between 23 and 34 weeks of gestation, administration of two doses of 12 mg of betamethasone, 24 hours apart, and administer a booster dose of 12 mg weekly for those patients who continue to be at risk of delivering prematurely. Beyond 34 weeks, steroids are used only when an amniocentesis is indicated and the lecithin/sphingomyelin (L/S) ratio shows persistent lung immaturity.

## DELIVERY ROOM MANAGEMENT

The basic principle guiding successful management should be directed toward prevention of any physiologic deviation from normality, such as hypothermia, acidosis or hypoxia. At the same time, it is important that each intervention during the resuscitation process be adapted carefully to the size and the needs of the tiny infant. Brisk maneuvers, excessive positive pressure with bagging or inappropriate administration of drugs and fluids can induce permanent central nervous system (CNS) or lung injuries.

During the initial steps of stabilization, the condition of the infant is assessed rapidly. After drying, positioning on warm blankets, and suctioning, most of the LBW infants require immediate initiation of intermittent positive-pressure ventilation with a bag and mask. For the LBW infants, ventilation is more effective if performed at a higher ventilatory rate than for the term infant. We use anesthesia bags and ventilate at a rate of 60–80 breaths/min, adjusting the pressure to provide adequate bilateral air entry. For extremely premature infants, intubation in the delivery room may follow rapidly. Because NICU is adjacent to the delivery room, if the infant is responding well to manual ventilation (heart rate >100, pink color), he or she is transferred to the NICU for further management.

Even following optimal resuscitation, the Apgar scores of LBW infants rarely exceed 6 or 7 in view of their decreased tone and reactivity, poor respiratory effort and initially poor peripheral perfusion. The infant's heart rate is thus the best measure of the effectiveness of resuscitation efforts.

## ADMISSION TO THE NICU

It is well established that the majority of cerebral injuries occur around the time delivery or in the immediate postnatal period. Acute changes in cerebral blood flow may predispose the very fragile network of periventricular vessels to rupture. Hence, it is essential to handle these fragile infants with extreme care, avoiding unnecessary disturbances, and preventing rather than correcting physiologic deviations in acid-base balance, blood gases, blood pressure or body temperature. During the first hours after admission, the premature infant is placed in an open radiant warmer to allow for easier access.

Blood is analyzed for glucose, electrolytes, blood gases, hemoglobin, and leukocytes. An intravenous (IV) with 10% dextrose is initiated at a rate varying from 85–100 mL/kg/day, according to the degree of immaturity and the type of incubator used (radiant heater vs. closed incubator).

Total parenteral nutrition (TPN) is generally started after the first 48 hours of life, when electrolytes, glucose, urea and acid-base status are well controlled. When the mother receives IV fluids during her labor, a baseline electrolyte profile of the newborn shortly after birth seems to be the proper way to follow the subsequent changes.

Electrolytes are repeated between 12 and 18 hours of age. During the first 72 hours, the body weight is recorded every 8 hours, and fluid intake is adjusted accordingly.

In order to establish prognostic criteria, it is important to obtain a cranial ultrasound in the first 24 hours of life. This ultrasound needs to be repeated at least 1 week later, or as often as necessary, depending on the pathology detected on admission or if the infant's condition has deteriorated, suggesting CNS involvement.

## RESPIRATORY SUPPORT

The introduction of exogenous surfactant therapy has reduced significantly the mortality of all newborns suffering from respiratory failure secondary to RDS, but its impact has been particularly important among the most premature infants.

Administration of surfactant in these very tiny infants requires extra care, as rapid changes in lung compliance may not only damage the lungs by creating overinflation and overdistension, but also may predispose to acute changes in ductal circulation which, in turn, could lead to both cerebral and or pulmonary hemorrhage. With rapid improvement in oxygenation, persistent hyperoxia also may be detrimental to the eyes. Hence, the administration of surfactant should be performed by an experienced person, under close monitoring of ventilatory parameters and rapid reduction of peak inspiratory pressures (PIP) and oxygen concentrations.

In RDS, there are compartments in the lung with relatively normal ventilation perfusion ratios and others with poor ventilation and adequate perfusion, it seems reasonable to attempt to improve ventilation of the poor ventilation perfusion (V-Q) compartment without overdistension of the normal V-Q compartment. Raising the ventilatory rate, which raises the mean airway pressure without changing the PIP, appears to accomplish this goal.

When the oxygen requirement exceeds 40% or the initial X-ray shows severe RDS, we immediately administer exogenous surfactant and rapidly adjust the ventilatory parameters according to the new lung compliance.

The concept of permissive hypercapnia for patients requiring mechanical ventilation gives priority to the prevention or limitation of severe pulmonary hyperinflation over the maintenance of normal ventilation. The principle consists of allowing the  $PCO_2$  to rise by minimizing ventilator pressures and tidal volume. Potential risks of high  $PCO_2$  values include increased cerebral perfusion, increased retinal perfusion, increased pulmonary vascular resistance, and reduction of pH. Based on epidemiologic observation, it appears that respiratory acidosis, unlike metabolic acidosis, is not associated with poor neurologic outcomes.

## CARDIOVASCULAR SUPPORT

By far, the major cardiovascular problem in extremely low birth weight (ELBW) infants is the presence of a PDA. More than 50% of infants born weighing less than 1,000 g will have a PDA diagnosed during the first few days of life. The onset of clinical manifestations of the PDA is related to the timing of improvement of the infant's respiratory status, which is associated with decreasing pulmonary vascular resistance and predominantly left-to-right shunt. However, the patency of the



ductus arteriosus can be documented easily in the first hours of life, with the help of echocardiography. At this early stage of life, the shunt is either right-to-left or bidirectional, depending on the severity of the infant's respiratory condition.

An active pericardium, with bounding pulses and visible carotid pulse, often will precede auscultation of a murmur. If left untreated, the infant may develop left-sided heart failure and pulmonary edema or Hemorrhagic pulmonary edema, with significant deterioration of the respiratory status. Significant left-to-right ductal shunting may cause decreased peripheral perfusion and oxygen delivery. ELBW infants with significant PDA are at risk of IVH, NEC, renal failure, CLD and metabolic acidosis.

Left-to-right shunting along with patent ductus leads to development of bronchopulmonary dysplasia. It prolongs the ventilator dependency. The diagnosis is confirmed by contrast ECHO.

Restriction of fluid therapy and administration of diuretics will help in managing the ductus. If the ductus persists after fluid restriction indomethacin is given in the dose of 0.2 mg/kg/dose for three doses at 12 hourly intervals is safe and effective. This will help in more than 70% of cases.

Contraindications to indomethacin therapy are renal failure, active bleeding, thrombocytopenia, and severe indirect hyperbilirubinemia. The presence of IVH does not appear to be an absolute contraindication to the use of indomethacin. Recent studies indicate that there is no progression of the severity of IVH after administration of indomethacin for PDA closure.

## FLUID AND ELECTROLYTES

It is important to remember that the body of the ELBW infant is made up of 85–90% water, which is distributed as one-third intracellular water (ICW). Immediately following birth glomerular filtration rate and fractional excretion of sodium (FENa) are low and urine output is minimal. This is followed by the diuretic phase, which results in a decrease in the extracellular compartment.

Once the infant's respiratory status has stabilized and the need for ready access to the infant is not as essential as it is during the hours following admission, the infant is transferred to an incubator maintaining 75–80% humidity for the 1st week of life. This approach allows limitation of fluid intake to between 80 and 100 mL/kg/day for the 1st day of life. In addition, we monitor the infant's weight every 8 hours during the 1st day of life and adjust fluid intake consequently.

Electrolyte abnormalities such as hyponatremia, hyponatremia, and hyperkalemia frequently are seen in LBW infants. Hyponatremia is usually the result of severe insensible water loss, but can be secondary to the treatment of metabolic acidosis with large amounts of sodium bicarbonate. Hyponatremia (<130 mmol/L) more frequently is seen because of the high fractional excretion of sodium (FeNa) during the diuretic phase.

On admission, infants receive only 10% dextrose solution in water. We monitor blood glucose and electrolytes closely and we test all urines for glucose. We subsequently adjust the IV dextrose according to the blood glucose values. We start sodium supplementation only when its serum value is less than 140 mmol/L, which usually happens between the 2nd and 3rd days of life.

## NUTRITION

Nutrition is an essential part of the care of the ELBW infant. These tiny infants are born with very low reserves of fat and carbohydrates, and they rapidly develop nutritional deficiencies in calcium, phosphorous, iron, trace minerals, and vitamins. Their endocrine and enzymatic capability is limited due to immaturity. Postnatally, they rapidly enter a catabolic state unless sufficient nutrients are given. But reversal of this catabolic state often is difficult because of limited feeding tolerance. The gastrointestinal tract (GIT) is immature in terms of digestive pathways and motor function, increasing the risk of developing NEC.

Because the first goal of nutrition is to prevent catabolism, usually this will be achieved by providing a minimum of 50 kcal/kg/day growth will require additional caloric intake. Achieving steady growth is essential for the LBW infant, because the growth velocity at 25–30 weeks' gestation is relatively higher than at term. If reasonable caloric intake cannot be provided, catch-up growth may never be achieved.

In the early days of life, satisfactory nutrition can never be achieved exclusively with milk. Parenteral nutrition provides the additional calories. In contrast to oral nutrition parenteral administration of 80–85 kcal/kg/day can provide the necessary calories for growth. When the infant no longer is receiving IV nutrition, 100–120 kcal/kg/day are needed to maintain growth. Appropriate growth, if one wants to mimic intrauterine growth, should be a 2% daily increase in body weight, slowing to 1% near term.

Both parenteral nutrition and oral nutrition are not without difficulties and complications in the LBW infant. TPN requires IV access and this can be associated with a variety of infections. Exclusive IV nutrition affects the mucosal lining of the GIT, which is bypassed and eventually may lead to villus atrophy. TPN also requires regular metabolic monitoring for glucose, electrolytes urea, lipids, and acid-base balance. Cholestatic jaundice is a frequent complication of TPN.

Enteral nutrition may consist of either breast milk or premature formulas. During fetal life, the fetus constantly swallows amniotic fluid, promoting intestinal development.

Enteral feeding, even in small amounts, has been demonstrated to stimulate trophic factors and hormonal maturation of the GIT, thus improving overall intestinal function and potentially improving feeding tolerance and preventing mucosal atrophy. Whether early introduction of feedings and stimulation of the GIT could prevent or decrease the incidence of NEC has not yet been established. Breast milk contains lipase, which improves fat tolerance.

Feeding difficulties are common in babies under 34 weeks of gestation. The babies do not suck. They have poor gag reflex. So, care should be taken to avoid aspiration. If baby is unable to take feeds by mouth, then nasogastric tube feeds are given. Oral iron started after 2nd week.

Neonates weighing less than 1,200 g or gestational age less than 30 weeks, IUGR infants should be started with IV fluids initially. Total parenteral nutrition is administered through the central line.

The 10% dextrose solution in the initial dose of 60 mL/kg body weight is started. Blood glucose level is checked every 3 hours. If it is more than 7 mmol/L, IV fluid is changed to 5% dextrose. Amino acids are added up to 25%, if IV fluids are required for more than 3 days.

Oral feeds are started if the bowel sounds are heard or once the meconium is passed. It usually takes about 2–3 days. But by the end of the 1st week, combined IV and enteral feeds should amount about 120–150 mL/kg body weight.

Neonates weighing 1,200–1,800 g or gestational age maturity is 30–34 weeks, should be put on gavage feeds. LBW babies weighing more than 1,800 g or gestational age maturity of more than 34 weeks should be given breast milk directly.

Breastfeeding alone contains insufficient nutrients for babies under 1,500 g. Hence, suitable supplements such as medium chain triglyceride, glucose polymer, phosphorus and sodium should

be given. Hyperbilirubinemia is treated by phototherapy and exchange transfusion.

## **GLUCOSE, CALCIUM AND PHOSPHORUS HOMEOSTASIS**

Early hypoglycemia frequently is seen in this group of infants, because of poor glycogen reserves and the immaturity of the postnatal adaptive mechanism of endocrine as well as enzymatic control of glucose. In particular, ketogenesis and lipogenesis, which lead to the production of alternate fuels, is limited in very premature infants, making the infant more dependent on glucose. Hence, an infusion of dextrose at the rate of 5–7 mg/kg/min is necessary to maintain normoglycemia.

Hyperglycemia is a frequent and challenging complication, particularly in extremely immature infants of 23–24 weeks of gestation.

The sudden onset of a glycosuria in a previous stable infant may be an early sign of infection. Hyperglycemia is also seen frequently with initiation of dexamethasone therapy for BPD. Because of the slow metabolic adaptation of the LBW infant, rapid and significant changes in glucose intake should be avoided in order to prevent episodes of hypo- or hyperglycemia, which can become difficult to control. Finally, for the treatment of acute and severe hypoglycemia, a bolus of no more than 200 mg/kg of dextrose can be administered as needed, while at the same time, increasing the concentration of the IV glucose infusion.

Because hypocalcemia also can induce apnea, we always verify calcium levels after the first 24 hours of life. It is important to remember that metabolic acidosis can give falsely reassuring values of ionized serum calcium, which decline rapidly with the improvement of acid-base balance. Mechanisms involved in the early manifestations of hypocalcemia include parathyroid dysfunction, renal immaturity and calcitonin stimulation. Our treatment of hypocalcemia consists of administering 500 mg/kg/day of calcium gluconate. As soon as we introduce TPN 300 mg/kg/day of calcium gluconate is added daily to the solution, together with multivitamins.

It is important to mention at this point that both the classic and hypophosphatemic forms of rickets nowadays are seen only in nutritionally neglected LBW infants.

## **ACID-BASE BALANCE**

Acid-base homeostasis varies in relation to the degree of renal maturity. The renal threshold for loss of bicarbonate can be as low as 15 mEq/L;

hence, there is often a need for more buffer with sodium bicarbonate in ELBW infants. The need for supplemental sodium bicarbonate also is frequent during the introduction of amino acids in the TPN.

Although acidosis is the main concern in the early days of life, later on, many of these tiny babies may develop a metabolic alkalosis due to the administration of diuretics, in combination with fluid restriction.

## JAUNDICE

Hepatic immaturity and reduced erythrocyte lifespan, blood group incompatibilities, extensive extravasation of blood, and increased entero-hepatic circulation due to poor bowel motility—all contribute to the fact that LBW infants are very prone to develop jaundice.

Because the serum bilirubin binding capacity is decreased in premature infants due to the lower serum albumin, the level at which toxicity for the brain and acoustic nerves may occur is much lower than that of the more mature infant. When the bilirubin level approaches the exchange transfusion level, it is important to void variations in acid-base balance, high levels of lipid infusion, hypothermia and certain medications which may compete with and displace bilirubin from albumin, thus precipitating kernicterus.

## INTRAVENTRICULAR HEMORRHAGE

The IVH is a major and unfortunately frequent complication in the LBW infant. Its incidence is correlated with the degree of prematurity. Potential complications of IVH include hemorrhagic periventricular infarction, hydrocephalus, periventricular leukomalacia (PVL), and seizures.

Intraventricular hemorrhage may present acutely, leading to shock and death; it may be clinically silent; or more commonly, it may present with cardiorespiratory instability.

The incidence is indirectly proportional to low birth weight of the babies. Many of the bleeds are asymptomatic. Hence, the routine cranial ultrasound is used for scanning. This should be performed at 24th, 3rd day and 7th day. Prevention is the ideal way of management. This includes preventing birth asphyxia, correcting, bleeding diathesis will help in preventing IVH, patent ductus arteriosus.

The immediate management of IVH involves stabilization of the cardiovascular system, correction of any bleeding diathesis, if present and monitoring for hyperbilirubinemia and hyperkalemia. Careful neurologic examination and serial measurement

of head circumference and serial cranial ultrasounds must be performed to allow early detection of hydrocephalus. If there is rapidly progressive dilatation of the ventricles, neurosurgical intervention may be necessary for temporary or permanent drainage of the cerebrospinal fluid.

## PERIVENTRICULAR LEUKOMALACIA

The PVL has been reported in varying incidence from 4 to 15% and is the consequence of hypoxic-ischemic lesions, leading to necrosis of the white matter. Most commonly affected is white matter near the trigone of the lateral ventricles and around the foramen of Monro. PVL may occur in association with IVH, but also may be diagnosed independently as the only CNS lesion.

Cystic PVL among preterm infants is the single best predictor of adverse long-term neurologic outcomes.

The diagnosis of PVL is made by cranial ultrasonography. When the lesions have occurred in utero, it is possible to make the diagnosis soon after birth. However, for postnatally-acquired PVL, several weeks may be necessary before the diagnosis can be secured. The characteristic evolution of PVL is the formation of multiple echolucent cysts. Because of the delayed appearance of the cystic lesions, it is important, even for those infants with normal early cranial ultrasonography.

## SEIZURES

Compared to full-term infants, seizures are more difficult to diagnose clinically, which probably is due to cortical underdevelopment at early gestational age. The etiology of seizures in the LBW infant, as for the term, infant, may be related to CNS pathology, metabolic derangements (i.e., hypoglycemia, hypocalcemia, and severe hyponatremia), infectious causes and drug withdrawal.

The order of preference for medications to control seizures is as follows:

- Phenobarbital at a loading dose of 20 mg/kg, which on occasion, can be increased to 30 mg/kg
- Phenytoin at a loading dose of 15 mg/kg
- Paraldehyde rectally at 0.3 mL/kg (diluted 1:1 in mineral oil)
- Occasionally diazepam at 0.1–0.2 mg/kg/dose

## HEARING IMPAIRMENT

Early diagnosis of hearing loss and the use of hearing aids as early as 6 months of age, together with speech therapy, are essential in order to

reduce the disability of deafness. The most objective tests are the measure of evoked auditory brain-stem responses or otoacoustic emissions.

## HEMATOLOGICAL DISORDERS

Low iron stores, multiple blood tests, blood loss due to either organ hemorrhage or hemolysis and rapid growth are some of the factors that make anemia a practically unavoidable hematologic complication for any LBW infant.

To decrease the risk of infection, one unit of packed red cells from a single, properly screened donor, divided into several small bags (satellite bags), could be used for the same infant.

## HOMEOSTASIS AND BLEEDING DIATHESIS

Conditions requiring immediate administration of additional vitamin K include hemorrhagic pulmonary edema, pulmonary or gastric hemorrhage and disseminated intravascular coagulation. The management of these conditions often will require, in addition to vitamin K, administration of fresh frozen plasma, transfusion of platelets and treatment of the underlying condition.

## APNEA OF PREMATURITY

Apnea of prematurity is a feature of nearly all infants with a birth weight less than 1,000 g. Its incidence and frequency decrease with advancing gestational age, but at times, it may be seen up to 42 weeks of gestation in the ELBWs population. It is a frequent indication for mechanical ventilation, thus exposing these infants to the potential complications of ventilatory support.

Apnea usually is defined as a cessation of breathing for 20 seconds or more, or of a shorter duration if associated with cyanosis or bradycardia. Different patterns have been observed in premature infants: central apnea (absent breathing movements) and obstructive apnea (central and obstructive).

LBW infants are particularly prone to obstructive apnea, especially when in the supine position with the neck in the midline, because of the weakness of the muscles of the oropharynx. Apnea due to obstruction of the lower airways also has been reported, suggesting of lung mechanics. The cessation of gas exchange during a significant apneic episode is manifested by hypoxemia and/or bradycardia. Recurrent episodes of apnea may affect neurodevelopmental outcome.

Patient management will depend on the severity and frequency of apneic episodes. Methylxanthines, which stimulate the respiratory center,

are the most effective pharmacologic treatment for apnea of prematurity.

Another drug that has been used for the treatment of apnea is doxapram. Like methylxanthines, doxapram has been observed to improve minute ventilation and tidal volume, lower PCO<sub>2</sub> and increase blood pressure.

## NEONATAL INFECTIONS

As the clinical signs of infection often are non-specific, the index of suspicion and the concern about the possibility of intrauterine infection should be very high in the presence of a premature birth. Hence, screening for infection should be an integral part of the evaluation of the LBW infant.

Diagnosis of neonatal infection sometimes can be difficult, as early neonatal infection often manifests with respiratory symptomatology, which is also the overwhelming pathology of prematurity. Early appearance of recurrent apnea, poor perfusion, hypotension, and significant metabolic acidosis, often in the presence of an abnormal leukocyte count, are very strong elements in favor of infection.

If the infant's condition improves rapidly, the blood culture is negative and the acute phase reactants are normal, antibiotics can be discontinued after 3–5 days.

## FOLLOW-UP

- All the danger signs should be explained to parents and informed to report in case of development of any danger sign
- Difficulty in feeding
- Reduced activity
- Baby is too cold or too warm
- Fast breathing and chest indrawing
- Abnormal movements
- Jaundice

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# Respiratory Distress Syndrome

## PRESENTING COMPLAINTS

A newborn (6 hours) baby was brought with the complaints of:

- Breathlessness since birth
- Bluish color since birth
- Indrawing of chest since 1 hour

## History of Presenting Complaints

The newborn baby was referred to neonatal intensive care unit (NICU) from pediatrician who attended the delivery. Boy was born at preterm at 35 weeks. The age of the mother at the time of the delivery was 18 years.

Baby was delivered vaginally at 35 weeks of amenorrhea. Boy was delivered normally without any intervention. Apgar score at 1 and 5 minutes were 4 and 8, respectively. Child required resuscitative intervention such as bag and mask

ventilation to establish spontaneous respiration. Baby was given oxygen at the rate of 4 L to maintain oxygen saturation up to 95. There was tachypnea with respiratory rate of 50 per minute. But there was no indrawing subcostal recession. Attending pediatrician discussed the case with senior doctor and then referred to NICU.

Mother was not booked for antenatal health check-ups. She was very irregular to antenatal health check-up. She never had any antenatal investigation. In the third trimester, she noticed swelling of the legs. When she was shown to the doctor, hypertension was diagnosed in her. She was on antihypertensive medication.

## EXAMINATION

The newborn child was lying in the bed with respiratory distress. Features suggestive of intra-uterine growth retardation (IUGR) were present. There was sternal retraction, intercostal indrawing, expiratory grunt, tachypnea. Child was on oxygen at a rate of 4 L to maintain oxygen saturation of 98.

The anthropometric measurements included, the weight was 1,500 g (<3rd centile), length was 48 cm (<10th centile), and the head circumference was 33 cm. Child was afebrile. The heart rate was 146 per minute and the respiratory rate was 80 per minute. The blood pressure recorded was 50/30 mm Hg. There was no pallor, no cyanosis, and no lymphadenopathy. Acrocyanosis and bluish discoloration over the tongue was present.

Respiratory system revealed presence of crepitation at both base. Per abdomen examination showed mild distension. Cardiovascular system revealed presence of tachycardia, no features suggestive of congenital heart disease.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 14,000 cells/cu mm
DC	: $P_{71} L_{25} E_2 B_2$
Blood sugar level	: 70 mg/dL

### CASE AT A GLANCE

#### Basic Findings

Length	: 48 cm (<10th centile)
Weight	: 1500 g (<3rd centile)
Temperature	: 37°C
Pulse rate	: 146 per minute
Respiratory rate	: 80 per minute
Blood pressure	: 50/30 mm Hg

#### Positive Findings

##### History

- Primi
- Young mother
- Difficulty in breathing
- No antenatal check-up
- Maternal hypertension

##### Examination

- Tachypnea
- Respiratory distress
- Grunting
- Low birth weight (LBW)
- Preterm delivery
- Basal crepitation
- Abdominal distension

##### Investigation

- Chest X-ray: Reticular granular pattern



Platelet count	: 300,000 cells/dL
Electrolyte	: Na—110 mEq/L K—4 mEq/L Cl—80 mEq/L
Blood group and Rh typing	: O positive
Chest X-ray	: Reticular granular pattern
Blood culture and sensitivity	: Sterile
Urine culture and sensitivity	: Sterile
ABG	: pH—7 PaCO <sub>2</sub> —55 mm Hg PaO <sub>2</sub> —45 mm Hg HCO <sub>3</sub> —18 mEq/L

## DISCUSSION

Neonatal respiratory distress syndrome (RDS) is the most common cause of respiratory failure in preterm infants. Its incidence is inversely related to gestational age and increases to as high as 95% in infants born at 22–24 weeks of gestation.

Hyaline membrane disease (HMD) is the important cause of respiratory distress in newborn. It occurs as a result of deficiency of surfactant. The name is derived from amorphous material that lines the terminal bronchiole and alveoli in this disease. Pathologically, there will be diffuse alveolar atelectasia, edema and cell injury. It is the most common cause of death before 30 weeks.

## INCIDENCE

- A ratio of lecithin/sphingomyelin (L/S):
  - <1.5—70%
  - 1.5–2.0—40%
  - 2—unlikely
- Incidence is more in male, especially in cases with prematurity, perinatal asphyxia, maternal diabetes, cesarean section, not in labor.
- Incidence is reduced in stressful pregnancy such as eclampsia and infection, maternal drug addiction, IUGR and corticosteroid administration prior to the delivery.

## ETIOLOGY

- *Prematurity:* Surfactant appears in the lung in the third trimester hence, the preterm infant, i.e., delivered before the term will not have sufficiently developed surfactant.
- *Asphyxia:* Acidosis, hypothermia and hypoxia will inhibit surfactant synthesis. This is more important in premature children.

- *Maternal diabetes:* There is increased incidence of RDS in infants of diabetic mother. The simple rationale in infant is delivered by cesarean section without having been in labor.
- *Cesarean section:* During the process of labor there will be increased activity of adrenergic system. This will help to release surfactant. This phenomenon is not available to the infants born with cesarean section.

The main feature of RDS is compromised lung function caused by both structural and biochemical immaturity of the lung.

## Structural Immaturity

Lung development during fetal life occurs in different stages. Following organogenesis in the first two stages (i.e., embryonic and pseudoglandular) of lung development, the canalicular stage, starting at approximately 16 weeks after conception, is the first step in lung differentiation, involving formation of an actual air-blood barrier. Differentiation continues in both the saccular and alveolar stages of lung development starting at 24 and 36 weeks' postconceptional age, respectively. This means that, at the time of birth, lung development of most preterm infants is still at the saccular stage, resulting in a reduced surface area for gas exchange and limited diffusion capacity due to thickened membranes at the air-blood interface.

## Biochemical Immaturity

The hallmark of RDS is a deficiency of pulmonary surfactant, a complex mixture of lipids (90%) and proteins (10%) that is synthesized in alveolar epithelial type II cells. Type II cells are one of the two epithelial cell types that line the alveolus. The most important function of surfactant is lowering of the alveolar surface tension, the force directed from the wall to the center of the alveolus at the air-liquid interface. This function is mainly attributed to the surfactant phospholipid dipalmitoylphosphatidylcholine and the surfactant hydrophobic proteins B and C. The hydrophilic surfactant proteins A and D play a role in innate host defense. Synthesis and storage of surfactant begins at about 16 weeks' gestation, and lung homogenates have high concentrations of surfactant by 20 weeks. However, surfactant is not secreted until later, appearing in amniotic fluid at approximately 28 weeks' gestation, although this may vary greatly among individuals. This explains why some infants with a gestational age of less than 30 weeks do not develop neonatal RDS while

other infants, born at a more advanced gestation, do.

The high alveolar surface tension accompanying surfactant deficiency will increase the elastic recoil forces of the lung and decrease compliance of the respiratory system. As a result, preterm infants with RDS need to create large transpulmonary pressures to establish an adequate tidal volume. The absence of surfactant will also compromise lung volume stability, especially at the end of expiration. This makes the lung prone to a low end-expiratory lung volume and atelectasis, partly because the highly compliant chest wall is unable to counteract the increase in elastic recoil forces of the lung. A low end-expiratory lung volume may further compromise lung compliance and increase airway resistance and pulmonary vascular resistance. Due to the fact that the hypoxic pulmonary vasoconstriction response is often not functional in newborns, perfusion of collapsed sacculi-alveoli, also referred to as intrapulmonary right-to-left shunt, increases and results in (severe) hypoxemia.

### Predisposing Factors

As mentioned, the incidence of RDS is inversely related to gestational age. It is twice as common in males as in females at all gestational ages and is more common in white infants. Delivery by cesarean section, particularly if performed before the onset of spontaneous labor, is an independent risk factor as well. Infants of diabetic mothers are five times more likely to develop RDS than infants of nondiabetic mothers with the same gestational age, sex, and mode of delivery. A higher maternal age also predisposes for RDS. Finally, the second-born twin is more likely to be affected, and a family history of RDS increases the risk for any given premature infant.

On the other hand, complications of pregnancy, such as pregnancy-induced hypertension, chronic maternal hypertension, premature rupture of membranes, intrauterine infection, and subacute placental abruption, all decrease the incidence of RDS. Infants born to mothers addicted to narcotics are also at less risk for developing RDS.

### Risk Factors for HMD

- Prematurity
- Male sex
- Cesarean section
- Maternal diabetes
- Second-born twins
- Perinatal asphyxia

### FACTORS WHICH HASTEN THE LUNG DEVELOPMENT

- Toxemia in mother
- PROM
- Glucocorticoid

### PATHOLOGY

Pathologic findings early in the course of RDS include atelectasis, pulmonary edema, pulmonary vascular congestion, pulmonary hemorrhage, and evidence of direct injury to the respiratory epithelium. Epithelial cell injury is especially evident in the bronchiolar region of the lung. Histologic findings include the presence of hyaline membranes, the characteristic eosinophilic material derived from bronchial and bronchiolar injury to epithelial cells. Pulmonary edema, hemorrhage and hemorrhagic edema are common pathologic features in RDS, especially if the clinical course is further complicated by patent ductus arteriosus (PDA) and congestive heart failure.

At postmortem examination, the lungs from infants with RDS are firm and airless. Atelectasis is striking on gross inspection, when the lungs are fixed in inflation, only the airways and a few alveolar ducts are air filled. Diffuse atelectasis and dilated terminal bronchioles and alveolar ducts lined with a homogeneous hyaline-staining material characterizes the microscopic picture.

The hyaline membranes are plasma clots containing fibrin, other plasma constituents, and cellular debris. The small pulmonary arterioles appear constricted. There is congestion of pulmonary capillaries and veins and an increase in pulmonary water with dilation of the lymphatics. Because of these histological features, RDS was initially named hyaline membrane disease.

Interstitial air leaks are common, and collections of air are often seen around small airways and vessels. In some cases, the alveoli and hyaline membranes contain red cells. Electron microscopic examination shows degeneration of epithelial and endothelial cells and rupture of the basement membranes. If death occurs after 3 or 4 days of respiratory distress, the hyaline membranes are fragmented and numerous macrophages appear in the intra-alveolar spaces. The pulmonary interstitium is widened and filled with round cells and fibroblasts. After the 1st week, there is a proliferation of alveolar epithelial type II cells and capillaries. In severe cases, chronic changes occur, including metaplasia of the bronchiolar epithelium and interstitial fibrosis.

## **PATHOPHYSIOLOGY**

Normally surfactant begins to reappear in the lungs from 36 to 48 hours of age, hence the condition worsens during the first 24 hours. Later, once the surfactant appears, it starts improving.

Histologically, there will be interstitial congestion of the alveolar wall. This causes desquamation of alveolar pneumonocytes. Alveolar ducts are dilated. There will be exudation of plasma into the alveoli. This again compromises with surface tension. Hyaline membrane is formed over the respiratory bronchioles and alveoli. This occurs as a result of coagulation of proteins of plasma exudate.

These changes lead to collapse of alveoli and stiffness of the lung. Lung compliance is decreased by 25%. Hence, there will be increased work of breathing. There will be increased pulmonary shunting producing, hypoxia, hypoventilation, and respiratory acidosis.

Pulmonary artery pressure and right heart pressure remain at the fetal level. This leads to right to left shunt across the ductus arteriosus and foramen ovale. Resultant hypoxia will produce alveolar damage.

This causes transudation of fluid and peripheral edema. Hypoxia produces hypotension, low blood volume and hyperoxaemia. This depresses myocardium. Accumulation of lactic acid occurs from anerobic metabolism secondary to hypoxia.

The diuretic phase of RDS is characterized by 6–8 hours period of increased urine output. This occurs between 24 and 60 hours of life. The urine output is at least 80% of the intake. This phase heralds rapid improvement in lung function and recovery from RDS. Infants with delayed diuretic phase are more likely to develop bronchopulmonary dysplasia.

The characteristic clinical features of infants with neonatal respiratory distress are an expiratory grunt, tachypnea, intercostal and sternal retractions, and cyanosis. Grunting respiration is caused by a prolonged expiratory effort against a partially closed glottis. It is usually preceded by a strong inspiratory effort during which the intrathoracic pressure drops well below atmospheric pressure. During the prolonged expiration, intrathoracic pressure is maintained above atmospheric pressure. Infants do not grunt with every breath, and those with severe disease grunt most frequently. By maintaining a positive intrapulmonary pressure during most of the respiratory cycle, grunting probably helps to prevent atelectasis, which is one of the hallmarks of RDS.

Due to their decreased lung compliance, infants with RDS need to generate large transpulmonary pressures to establish an adequate tidal volume. The large negative intrathoracic pressures generated as the infant attempts to inflate its lungs cause the soft tissues of the chest cage to retract. These retractions are particularly notable in very small preterm infants as they have highly compliant chest walls. With severe respiratory distress, the lower sternum may be pulled in almost to the vertebral column by the forceful contraction of the diaphragm. Infants breathe primarily with the diaphragm and have very compliant chest walls; as a result they often have paradoxical breathing movements. Thus, as the chest caves in, its circumference becomes smaller while the abdominal circumference increases. As a result, breathing becomes less efficient and tidal volumes become smaller. By increasing their respiratory rate, the infants try to maintain an adequate minute volume as much as possible.

The combination of reduced alveolar ventilation and stability explains that breath sounds are often diminished in intensity and have a harsh, tubular quality. Occasionally, there are fine rales, particularly in those infants born by cesarean section who may have excessive lung liquid.

Cyanosis is an early sign of RDS and, as the disease progresses, may be present even when an infant breathes 100% oxygen. As the lungs become more difficult to ventilate, the work of breathing increases, the infant tires, and arterial carbon dioxide tension rises. At the same time, the hypoxemia and diminished peripheral blood flow cause metabolic acidosis as lactic acid accumulates. With the development of acidosis, potassium leaves the cells and its concentration in serum rises, in some instances to very high levels.

Urine output is usually diminished early in the course of the disease, and the infants may become progressively edematous. Some infants, especially very LBW infants, have systemic hypotension, peripheral pallor, slow capillary filling, and hypothermia when not treated in time with sufficient respiratory support and exogenous surfactant.

## **POSTNATAL LUNG MATURATION**

It takes only 1–2 days following birth for an immature lung to mature as it responds to the surge of glucocorticoids and  $\beta$ -adrenergic compounds released by the stress of delivery. Glucocorticoids increase surfactant synthesis, and  $\beta$ -adrenergic stimulation promotes its secretion. At the same

time, structural changes occur in the lung. Thin-walled respiratory units develop, and the number of capillaries increases. With these changes, the signs and symptoms of respiratory distress usually subside after 48–72 hours of life. Recovery is usually heralded by diuresis. Clinical improvement is accompanied by a rapid fall in pulmonary vascular resistance and a rise in systemic arterial pressure. In some infants, particularly the least mature with birth weight less than 1,500 g this may permit development of a large shunt from the aorta through a patent ductus arteriosus to the pulmonary artery. In these infants, recovery may be interrupted by the development of pulmonary edema.

## CLINICAL PRESENTATION

*Clinical examination:* This should include the assessment of severity of the disease as well as the cause of the distress (**Table 1**).

Obstructed breathing occurs due to Pierre Robin anomaly and is relieved by prone position. Child turning pink on crying and cyanosed on nose breathing is seen with choanal atresia. Froth in the mouth and cyanosis during the feed first indicate tracheoesophageal fistula. Pneumothorax and lobar emphysema will produce asymmetrical chest movements. Scaphoid abdomen and grossly shifted mediastinum suggests diaphragmatic hernia. Pink frothy tracheal fluid is encountered in pulmonary hemorrhage.

*Time of onset of respiratory distress:* Causes of the respiratory distress can be analyzed with the clue of time of onset of distress.

*Within 4–6 hours of birth:*

- Premature—HMD
- Term—meconium aspiration
- Any gestational age
  - Pneumothorax
  - Asphyxia
  - Transient tachypnea of newborn (TTN)
- Transposition of great arteries—failure to become pink

*After 4 hours:*

- Pneumonia
- Congenital heart
- Metabolic acidosis or lung malformation

## CAUSES OF CYANOSIS IN RESPIRATORY DISTRESS SYNDROME

- Ventilation-perfusion mismatch due to atelectasis secondary to surfactant deficiency
- Intrapulmonary shunting of the blood due to pulmonary vasoconstriction secondary to hyperoxemia and acidosis
- Shunting across the foramen ovale and ductus arteriosus
- Atelectasis
- Acidosis
- Surfactant deficiency

## CLINICAL FEATURES (FIG. 1)

The infant attempts to maintain alveolar volume by prolonging and increasing expiratory pressures by breathing against a partially closed glottis, causing the grunting noise characteristic of RDS, but often seen in other respiratory disorders as well. Increasing oxygen requirements and the need for ventilatory support often occur rapidly in the first 24 hours of life and continue for several days thereafter.

The clinical course depends on the severity of RDS and the size and maturity of the infant at birth. In uncomplicated RDS, typically seen in more mature infants, recovery is rapid and infants generally no longer require oxygen or ventilatory support after the 1st week of life. The most premature infants are at risk for severe RDS and frequently develop complications, including central nervous system (CNS) hemorrhage, PDA, air leak, and infection, which contribute to prolonged requirements for oxygen and ventilatory support.

The clinical signs to diagnose RDS include respiratory rate more than 60 per minute, sternal retraction, intercostal and subcostal recession. To confirm our diagnosis all these signs should

**TABLE 1:** Grading of the severity of respiratory distress.

Score	0	1	2
Respiratory rate	<60/min	60–80/min	>80/min
Cyanosis	No	No cyanosis at 40% O <sub>2</sub>	Require >40% O <sub>2</sub>
Retraction	No	Mild	Moderate-to-severe
Grunting	No	Audible with stethoscope	Audible without stethoscope
Air entry	Good	Decreased	Nonaudible

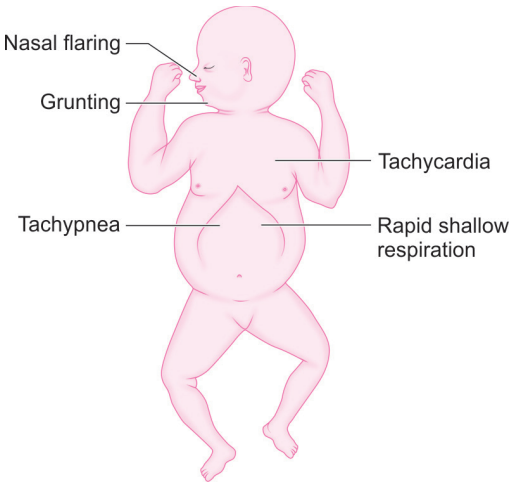


Fig. 1: Clinical features.

TABLE 2: Lung function test in RDS.

Measurement	Normal	RDS
Lung compliance (mL/H <sub>2</sub> )	5–6	0.8–1.5
Forced residual capacity (mL/kg)	30	10–20
Tidal volume (mL/kg)	6–8	4–7
Alveolar volume (mL/kg/min)	200	250–350

appear within 4 hours of birth and should persist for more than 4 hours.

Altered lung function test is depicted in Table 2.

GENERAL FEATURES

- Preterm baby
- Intercostal and subcostal retractions
- Cyanosis
- Breathlessness
- Apnea

ESSENTIAL DIAGNOSTIC POINTS

- Respiratory rate more than 60/min
- Cyanosis
- Use of accessory muscles of respiration—nasal flaring, intercostal, and subcostal retraction
- Expiratory grunt
- Caused by respiratory and nonrespiratory causes

DIAGNOSIS

The clinical course, radiograph of the chest, blood gas and acid-base values help to establish clinical diagnosis. Chest radiograph shows characteristic reticular granularity of the parenchyma. The laboratory findings are characterized initially by

progressive hypoxemia, hypercarbia and variable metabolic acidosis.

LABORATORY SALIENT FINDINGS

- L/S ratio in amniotic fluid
- Gastric shake test
- Chest X-ray—reticular granular pattern
- ABG to confirm hypoxaemia, hypercarbia metabolic acidosis

CHEST X-RAY

This is the most useful investigation that can help in the etiological diagnosis of RDS in the newborn. The radiographic appearance of the lungs in infants with RDS is characterized by reduced aeration with a diffuse reticulogranular pattern of increased density, usually uniform in distribution but occasionally, more marked in the bases or on one side. The densities are due to miliary atelectasis and interstitial edema. Lung volumes are small, and even radiographs taken after a maximal inspiration rarely show the diaphragm to be below the eighth or ninth interspace. The heart is usually normal in size, although it often appears large because of the large thymic shadow and decreased lung volume. In RDS, the radiological features include symmetrical fine reticulogranular pattern, reduced lung volume, diffuse haziness (ground-glass appearance), air bronchogram, and complete white out of lungs in late stages.

In TTN, the chest X-ray shows normal or increased lung inflation, streaky perihilar infiltrates, and fluid in horizontal fissure. In MAS, chest X-ray shows hyperinflation, coarse irregular opacities, and sometimes pneumothorax. Air leaks, esophageal atresia, and diaphragmatic hernia can be diagnosed by typical radiological features.

DIFFERENTIAL DIAGNOSIS

- Group B streptococcal septicemia
- Cyanotic heart disease
- Persistent pulmonary hypertension
- Aspiration syndrome
- Diaphragmatic hernia
- Cystic adenomatoid malformation
- Pulmonary lymphangiectasia
- Transient tachypnea of newborn

TRANSIENT TACHYPNEA OF THE NEWBORN

It may be difficult to distinguish RDS from normal, physiological pulmonary transition after birth. During this transition, fluid needs to be cleared from the lung and an air-filled functional residual



capacity needs to be created. Preterm infants often show signs of respiratory distress, including grunting and retractions. Furthermore, some infants may be oxygen dependent. In some infants, pulmonary transition may take several hours, a condition also referred to as transient tachypnea of the newborn, or wet lung. However, in contrast to RDS, these symptoms are usually not progressive but instead resolve within the first 24–48 hours. Furthermore, the chest X-ray shows hyperaeration of the lungs, perihilar streaking and fluid in the interlobar fissures.

## CONGENITAL PNEUMONIA

Infants with congenital pneumonia, especially group B *Streptococcus* may also present with signs of respiratory distress that can be clinically and radiologically indistinguishable from RDS.

## TREATMENT

At the time of birth, most of the lung is still fluid filled, and the infant clears the fluid by creating large expiratory pressures, also referred to as expiratory braking. Clinically, expiratory braking often presents itself as grunting and retractions. Due to the fact that fluid clearance takes time, most infants are cyanotic at birth and it takes them up to 10 minutes to attain oxygen saturation ( $\text{SpO}_2$ ) of 90% or more. It is clear that normal physiological pulmonary transition may be difficult to distinguish from RDS. For this reason, the initial treatment should be similar and consist of supporting the infant without causing injury to the vulnerable lungs.

The main aim of treatment is to keep the baby alive and in good condition. This should continue until he starts synthesizing his own surfactant. Hence, any condition which inhibits surfactant synthesis should be managed carefully.

If the infant is spontaneously breathing, the expiratory phase of respiration should be supported with CPAP. If spontaneous breathing is absent or inadequate, positive-pressure ventilation should be initiated. If clinical signs of respiratory distress and cyanosis persist after the transitional phase, RDS is very likely and appropriate treatment should be started.

The primary aim in treatment of RDS is to restore lung function and gas exchange while avoiding treatment-induced injury to the vulnerable lungs of preterm infants. As low end-expiratory lung volume is the most prominent feature of RDS, stabilizing end-expiratory lung volume should be the first goal of treatment.

The following parameters should be monitored continuously in all babies:

- $\text{PaO}_2$  level by umbilical artery catheter (UAC) or by transcutaneous every 4–6 hourly
- Arterial blood gas (ABG)
- Fractional inspired oxygen concentration
- ECG
- Ventilator
- Electrolyte, calcium and albumin daily or twice daily
- *Investigation:*
  - PCV
  - Chest radiography
  - Tracheal respiration for culture

Surfactant replacement therapy is provided through the endotracheal tube and is often used several times during the early course of RDS to maintain pulmonary function. Exogenous surfactants are given by intratracheal instillation of doses of approximately 100 mg of phospholipids per 1 kg of body weight.

## Supportive Treatment

- *Acid-base homeostasis:* It is necessary to keep infant's pH > 7.25.
  - *Metabolic acidemia:* It is diagnosed when there is base deficit of more than 5 mmol/L. It is very important to treat the etiology such as anemia, hypoxemia and sepsis. However, treatment of acidemia is important, when the base deficit exceeds 5 mmol/L. Spontaneous correction is expected in an infant who is stable, i.e., normally perfused and normotensive. Again after waiting for 2–3 hours, base deficit is measured, if there is no improvement sodium bicarbonate can be used. But the rate of infusion should be slow. It should not exceed 0.5 mmol/min. Dose can be calculated as follows:
 
$$\text{Dose} = \text{Base deficit (mmol/L)} \times \text{body weight (kg)} \times 0.4$$
  - *Respiratory acidemia and alkalemia:* Respiratory alkalemia is diagnosed when  $\text{PaCO}_2$  level is below 30 mm Hg. This in turn produces decreased cardiac output and cerebral blood flow and intraventricular hemorrhage (IVH). Most of the time it can be iatrogenic or over vigorous IPPV. A steady rise in  $\text{PaCO}_2$  with the help of ventilator is advised. A sudden rise will suggest pneumothorax. Atelectasis misplaces endotracheal tubes. Plasma expanders can be used at the dose of 10–20 mL/kg if the blood pressure is less than 30 mm Hg.

- **Feeding:** Oral feedings are withheld for first 2–3 days because of paralytic ileus. Many infants will pass meconium by third day. Bowel sounds will be present. Hence, 1 mL of expressed breast milk (EBM) hourly can be increased and if it is not tolerated, parenteral nutrition should be considered.
- **Fluid electrolyte balance:** Main aim is to take care of excessive fluid administration. Infant with RDS are prone to develop pulmonary edema because of presence of hypoalbuminemia and increased capillary leak. Fluid overload gives rise to necrotizing enterocolitis (NEC), PDA and chronic lung disease. Fluid intake is calculated or restricted to 60 mL/kg/day. Hypokalemia, hyperkalemia, and calcium hemostasis should be monitored and maintained. Infusion of dopamine (5–10 µg/kg/min) may help maintain the circulation and avoid excessive fluid administration, especially in the very LBW infant

To avoid opening of the ductus arteriosus by fluid overload, 60 mL/kg fluid should be given the first day, 80 mL/kg in the next 3 days. Glucose is given at the strength of 10–50%. Sodium, calcium, and amino acids are also added. Hypoalbuminemia is seen among premature infants. Peripheral and pulmonary edema will result if the albumin level is below 20 g/L. Hence, infusion of 0.5–1 g/kg is advised. Apprehension of the oligemia state in the first 24 hours of RDS can be alleviated by trial of furosemide at dose of 1.5 mg/kg.

Indomethacin is inhibitor of prostaglandin synthesis. This helps in closure of ductus arteriosus. The dose is 0.2 mg/kg orally or intravenously every 12 hourly for total of three doses. This is advised in infants with hypoxemia and congestive cardiac failure secondary to patent ductus arteriosus.

Hypotension is the feature in the first few hours of life. Systolic blood pressure should be maintained at 30–40 mm Hg. PCV should be recorded. If it is less than 40, blood transfusion is advised. If PCV is 45%, albumin is given. If still hypotension persists, dopamine 5–10 mg/kg/min is given intravenously.

### Surfactant Replacement Therapy

Surfactant deficiency; one of the main features of RDS, can be treated by exogenous surfactant replacement. Administering exogenous surfactant into the lungs will lower the surface tension, improve lung compliance, and stabilize end-expiratory lung volume.

### Timing of Surfactant Therapy

There are two clearly defined treatment strategies for administration of surfactant: (1) Prophylactic therapy, which requires the surfactant preparation to be instilled in the infant's trachea shortly after birth, preferably in the delivery room; and (2) Rescue therapy, which is designed to treat infants with established RDS. The later can be divided into early (<2 hours after birth) or delayed (2 hours after birth) rescue treatment.

More recent studies comparing invasive mechanical ventilation combined with prophylactic surfactant treatment to primary nasal CPAP and, if indicated, rescue surfactant treatment have shown that prophylactic treatment is associated with an increased risk of death or bronchopulmonary dysplasia (BPD). For this reason, prophylactic surfactant treatment is no longer recommended when using primary nasal CPAP at birth.

### Modes of Surfactant Delivery

Historically, surfactant was administered via an endotracheal tube during invasive mechanical ventilation. As the latter has been identified as a major risk factor for ventilator-induced lung injury and subsequent BPD, alternative, less invasive strategies of surfactant administration have been investigated.

During the INTubation-SURfactant-Extubation (INSURE) protocol, infants are intubated and surfactant is administered followed by immediate extubation to nasal CPAP. Compared with traditional surfactant treatment INSURE reduces the need for mechanical ventilation, but the effect on other clinical outcomes such as mortality and BPD at 36 weeks' postmenstrual age is limited. With the aim of avoiding intubation altogether, some investigators explored the feasibility of administering surfactant during spontaneous breathing on nasal CPAP. Several studies have now shown that this route of administration, often referred to as less-invasive surfactant application (LISA) or minimally invasive surfactant therapy (MIST) reduces the need for invasive mechanical ventilation and death or BPD at 36 weeks' postmenstrual age. Other modes of surfactant delivery, including the use of a laryngeal mask or nebulized surfactant administration, still need further evaluation.

Artificial surfactant, i.e., Exosurf in 67.5 mg phospholipids per kg administered gradually for over 15–40 minutes. Surfactant improves oxygenation by resolving atelectasis and improving lung compliance. Hence, it reduces the duration of

ventilatory support and decreases the incidence of air leaks.

Before stating the surfactant therapy, these should be adequate oxygenation and perfusion. The dose of the surfactant is 100 mg/kg (4 mL/kg). The route of administration is intratracheal. This is done by 5 Fr end-hole catheter. This tip of the catheter should come just beyond the endotracheal tube.

Repeat doses of the medicine may be administered depending upon the severity of the disease. Infant should be given 100% oxygen to aerolize surfactant into all the lobes of both the lungs. The therapy is followed by improved oxygenation this requires reduction of mean airway pressure and  $\text{FiO}_2$  to prevent development of air leaks, damage to retina and lungs. Endotracheal tubes are used. The frequent adverse effects are bradycardia, desaturation, apnea and pulmonary hemorrhage. Risk can be decreased by prenatal glucocorticoid therapy. Early postnatal PDA treatment is done by indomethacin or ligation.

## Oxygen Therapy

Aim of oxygen therapy is to keep  $\text{PaO}_2$  level at 60–90 mm Hg. Higher concentration will cause retinopathy of prematurity, pure oxygen administration is not advised. It inactivates surfactant and produces atelectasis and eventually produces pulmonary edema and hemorrhage. Purity of oxygen should limit to 95%.

Frequent checking of infant's  $\text{PaO}_2$  is always mandatory. Along with it acid-base status should be monitored. Umbilical artery catheterization is a widely used technique. Problems associated with the catheter block should be looked for. The findings of the catheter blocks are pale, mottled legs, discolored legs, hematuria and abdominal distension, and blood in the stool.

Warmed and humidified oxygen is used. This is very useful for mild-to-moderate RDS. This should be given by head box. If the oxygen concentration required is more than 60%, alternative form of oxygen is started.

## Continuous Positive Airway Pressure

Adequacy of ventilation and oxygenation must be established as soon as possible to avoid pulmonary vasoconstriction, further ventilation-perfusion abnormalities and atelectasis. Positive-pressure ventilation, CPAP and oxygen therapy may be required at any time during the course of RDS and must be readily available to the infant. Close monitoring of pH, oxygen saturation,  $\text{PCO}_2$

by transcutaneous monitors and by arterial catheterization or sampling of arterialized capillary blood is critical in guiding mechanical ventilation and ambient oxygen requirements.

This improvement in oxygenation has been linked to a higher end-expiratory lung volume. Recent studies have also shown that primary CPAP is the preferred mode of respiratory support after birth, as it reduces the need for invasive mechanical ventilation, surfactant treatment, and the risk of death or bronchopulmonary dysplasia.

Continuous positive airway pressure is usually administered via the nasal route using either a mask or prongs. Although the optimal level of CPAP still needs to be established, a continuous positive pressure of up to 6–10  $\text{cmH}_2\text{O}$  can be tolerated by the nasal route. Minimal invasive surfactant treatment and nasal intermittent positive pressure ventilation (IPPV) might further enhance the success of CPAP in patients with RDS. However, there is insufficient evidence to support the use of humidified high-flow nasal cannula as an alternative primary mode for CPAP in infants with RDS.

In cases in which nasal noninvasive support is not effective in restoring lung function and gas exchange or if severe apnea occurs, intubation and mechanical ventilation should be started using either conventional modes or high-frequency ventilation. Again, maintaining an optimal lung volume should be the primary ventilation strategy when using these modes.

Here the applied pressure is up to 8–10  $\text{cmH}_2\text{O}$ . This pressure keeps the alveoli open and preserves the surfactant. Splinting of the alveoli by pressure reduces the shearing forces.

Lung function shows improvement. Respiration becomes regular. FRC increases and airway resistance decreases. CVP is raised by 10–20%. Pulse pressure falls slightly.

The CPAP can be started with 8 L/min. The gas should be warmed and humidified. The level of the CPAP can be adjusted by tightening the gate clip. The conventional pressure monitor is used to check the amount of CPAP.

The CPAP is indicated when the  $\text{PaCO}_2$  is less than 60 mm Hg in recurrent apnea and during the weaning phase of ventilator. More effective CPAP is seen when it is started early. CPAP is more useful when the child requires oxygen at the concentration of 60–70%. It is useful in infants of less than 1.5 kg weight who need 30–40% oxygen during the first 24 hours of life. The initial pressure applied is 5–6  $\text{cmH}_2\text{O}$  of CPAP. Once the condition

improves CPAP is reduced to 1–2 cmH<sub>2</sub>O. Finally reduction is 2 cmH<sub>2</sub>O.

PaO<sub>2</sub> is checked for each change. Once the PaO<sub>2</sub> is satisfactory at the CPAP of 2 cmH<sub>2</sub>O, CPAP can be discontinued. If the same thing is maintained minimum for 4 hours and again if it deteriorates, CPAP can be restarted.

As forced inspiratory oxygen requirements decrease during recovery, airway pressure decreased and the infant is weaned to head hood or nasal cannula oxygen. Apnea, inadequacy of ventilation, atelectasis, mucous plugging, hyperaeration, or air leak may complicate the care of infants with RDS.

Nasogastric tube feeding is well tolerated. Oral feeds can complicate into regurgitation. IV fluid should be carefully monitored for the fear of fluid retention by retarding venous return.

## Intermittent Positive Pressure Ventilation

### Indications

- Electively in VLBW, i.e., <1000 g
- Blood gas analysis is poor
- Severe retraction
- Intractable apnea
- Laboratory indication—respiratory acidosis pH < 7.2
- Severe hypoxemia
- Clinical failure to establish effective ventilation, onset of apnea irregular and exhausted respiration
  - PaCO<sub>2</sub> > torr
  - PaO<sub>2</sub> < 50–60 torr

### Principle

Normal lungs require low pressure, i.e., 12–14 cmH<sub>2</sub>O to inflate. The inspiratory time is 0.2 second and expiratory time is 0.4 second (I:E—1:2). This is the time required for the lungs to inflate to 60% of its minimum. At this level, airway resistance and lung compliance coincide with each other, i.e., apnea of premature.

## Low Compliance of Lungs in RDS

It requires relatively more inspiratory to expiratory time to inflate lungs. It requires high inspiratory pressure with the positive end-expiratory pressure (PEEP) to keep alveoli open. This requires mean airway pressure of 12–14 cmH<sub>2</sub>O volume by rising the respiratory rate and tidal volume or lowering PEEP. High resistance as in meconium aspiration requires prolonged expiratory time, no PEEP and slow rate.

The aim of the IPPV is to keep PaO<sub>2</sub> level above 40 mm Hg and PaCO<sub>2</sub> level below 60 mm Hg. PaCO<sub>2</sub> level more than this produces IVH in an infant weighing less than 1.5 kg.

Endotracheal tube (ETT) number 3 or 3.5 mm diameter should be used. Oral ETT is used for shorter duration, i.e., for 24 hours. If the longer periods of IPPV is expected, nasal ETT are used. Outer margin of the ETT at the end of the nostril should be marked and fixed to avoid displacement. Immobilization of the tube is very important. Position of the tube is checked radiologically. Baby's head should be placed in slight extension. This will avoid trauma to laryngeal mucosa.

Small dead space should be maintained in the ventilator circuit and in baby. This will help to prevent atelectasis. Good humidifier is required. Suctioning of the ETT is repeated every 4 hourly. Swift and efficient suctioning is accepted. 0.5 mL of normal saline should be instilled before suctioning. Child should be observed during suctioning. Suctioning should be stopped immediately, if there is cyanosis, if PaCO<sub>2</sub> levels falls below 50 mm Hg, and if the heart rate is below 80.

## Initial Ventilator Settings

- *Respiratory rate:* 30–40 per minute  
*Inspiratory time:* 0.2–0.6 second  
In VLBW, 60–40 per minute may be more physiological. Baby synchronizes better with ventilator to give improved oxygen and pH. This will lower the incidence of pneumothorax.
- Peak pressure initially 25 mm Hg  
*I:E ratio:* 1:2  
*Gas flow rate:* 5–10 L/min
- Continuous distending pressure of 4–6 cmH<sub>2</sub>O to keep alveoli open
- Failure to synchronize with a ventilator may be an indicator for transiently raising inspiratory pressure or plasma infusion. If the infant's fighting continues, a high pressure of 30–40 cmH<sub>2</sub>O is continued for exceptionally stiff lung. Child may require sedation.

Ventilator setting is done according to the readings given:

<b>Ventilator settings</b>	
Rate	30–40/min
FiO <sub>2</sub>	0.8
Positive inflation pressure	25 cmH <sub>2</sub> O
Positive end expiratory pressure	5 cmH <sub>2</sub> O
I:E ratio	1:1::1.5:1
Gas flow per minute	5–10 L/min



*Subsequent alteration to ventilator settings:* This is in order of adjustment while improving ventilation to minimize atelectasis, bronchopulmonary dysplasia, and pneumothorax.

- $O_2$  is raised to not more than 95%.
- Altering I:E ratio can be prolonged, the inspiration raised  $PaO_2$  1:1. 1:2 for ventilating healthy lung.
- Respiratory rate is raised to reduce  $CO_2$  retention. Sometimes it is better to accept raised  $PaCO_2$  than increasing the peak inflation pressure.
- Raising the inflation pressure to 5  $cmH_2O$ .

Once these improve in the status, peak pressure is reduced. Oxygen and respiratory rate is reduced to minimize barotrauma, pneumothorax, and bronchopulmonary dysplasia.

Mechanical problems associated with the ventilator should also be kept in mind when there is no improvement in the child's condition.

- No chest wall movements-hand ventilation with 100% oxygen by bag and mask. Improvement indicates ventilator leak or stiff lung needing higher pressure. Poor or no response means tube higher pressure. Poor or no response means tube is partially or totally blocked and infant should be reintubated.
- If the chest wall is moving it means ventilator is working, then tube should be checked to know whether it is in right main bronchus. Adequate oxygen concentration rate of inflation pressures are monitored.
- If the child is still fighting nonsynchronized, then oxygen concentration is increased up to 95%. Respiratory rate is increased in steps like 10 per minute up to 60–90 per minute. Inflation pressure can be increased. If the child is still fighting then pancuronium is continuously used.
- If the child is still fighting to improve then pneumothorax, septicemia, hypotension, hypoglycemia should be suspected. Metabolic acidosis, NEC, and PDA should also be kept in mind.

$PaO_2$  is directly related to the mean airway pressure (MAP). MAP is the measure of the average pressure to which the lungs are exposed during the respiratory cycle. This can be calculated by dividing the area under the airway pressure curve by the duration of the cycle. The MAP is affected by the changes in the inspiratory flow, peak respiratory pressure and the ration of I:E. MAP can be measured directly from ventilator. Retention of  $CO_2$  occurs when there is slow respiratory rate,

short expiratory time, and high levels of PEEP. If there is hypercapnia and hypoxia PIP is increased until satisfactory gas analysis is obtained.

Optimal PEEP is the end-expiratory pressure at which oxygenation is minimum with the minimal effect of cardiovascular function. To determine this, PEEP is maintained at the level equal to 10% of the inspired oxygen concentration.

To improve oxygenation when  $PaCO_2$  is normal, i.e., 35–55 mm Hg, MAP is increased. PEEP is also increased. Inspiration should, however, rarely last longer than 1.5 seconds. I:E ratio is of no use.

To improve oxygenation when  $PaCO_2$  is less than 30–35 mm Hg, diagnosis should be rechecked. Other causes to be considered are CHD, persistent fetal circulation and over ventilation. Chest X-ray is helpful. If still the diagnosis is RDS, MAP should be sustained. When PEEP is increased, rate is decreased.

When there is hypercapnia, i.e., >70 mm Hg, it is managed by increasing the rate and decreasing the PEEP. PEEP should not be reduced below 3  $cmH_2O$  as it preserves the surfactant. Infant can be paralyzed by pancuronium.

In spite of all these maneuvers, if the blood gas analysis is not satisfactory, the following possibilities are suspected:

- Blocked or leaking tube
- Non-corrected metabolic and electrolytic imbalance
- Complications of RDS

For diagnosis in RDS, PIP and MAP are pushed until  $PaO_2$  is 50 mm Hg. This is used in children with  $CO_2$  retention. The disadvantage is air leak syndrome and chronic lung disease. Other method is increasing the fast ventilatory rate and this causes pulmonary vascular dilatation.

If all the procedures fail, the three most common diagnoses to be kept in mind are pneumonia or septicemia, massive IVH and primary pulmonary hypoplasia.

Once the reasonable, satisfactory blood gases are obtained this should be maintained for 3–4 hours. If PIP is more than 30  $cmH_2O$ , every attempt is made to bring it down. RDS tends to get worse for the first 36–48 hours.

As RDS resolves, the peak pressure is reduced in steps of 2–4  $cmH_2O$  and oxygen steps of 5–10% down to 40–45%.

## Antibiotics

As infant is on IPPV, antibiotics should be started. Some antibiotics are maintained until the infant is on IPPV or for 1 week after IPPV.



## Vitamin E

It is a biological antioxidant. This inhibits peroxidation of membrane lipids by the radical such as superoxide. It is advised in LBW babies receiving 100 per oxygen which will cause retrolental fibroplasias and bronchopulmonary dysplasia. The dose is 100 IU/kg/day intramuscular to maintain blood vitamin E level between 2 and 3 IU/dL.

## Sedation

Pancuronium is the drug for sedation. Indications for sedation are:

- Child fighting with ventilatory breath to avoid risk of pneumothorax.
- Child who requires greater than 75% of oxygen and or peak inspiratory pressure greater than 30 cmH<sub>2</sub>O.
- In case of fluctuation in BP, if untreated, infants may have increased IVH.

Position of the infant should be changed every 2–3 hourly. If this is done promptly, secretion is rarely a problem. ETT should be sucked out every 4–6 hourly instilling normal saline. Chest physiotherapy is done if the secretion becomes a problem.

## Weaning of IPPV

This process takes several weeks. Sometimes it will be completed within 24 hours. Weaning off is slower in LBW babies. Weaning process is started by reducing high pressure and oxygen concentration. Pressure is reduced at the rate of 2–3 cmH<sub>2</sub>O and oxygen concentration by 5–10% at a time. Such reduction step can be done once in 4 hours.

In VLBW, rate is reduced gradually, i.e., 15/min, 10/min, 5/min. Prolonged apnea is avoided. This will help infant to develop spontaneous respiratory effort. While reducing the rate, the inspiratory time should never exceed 1 second. This is known as intermittent mandatory ventilation.

While changing to CPAP, forced inspiratory oxygen level should be increased to 0.05–0.1. This is because infant may become transiently hypoxia or apneic during or after transfer. After changing there will be immediate surge in PaO<sub>2</sub> because of increased FiO<sub>2</sub>. Hence it is necessary to check PaCO<sub>2</sub>, 30–60 minutes after the transfer to CPAP.

*Causes of failure of weaning of IPPV:*

- PDA with pulmonary edema
- Secretions

- Laryngeal edema and stenosis
- BPD
- Recurrent apnea

## Extubation

When the child's condition is good, chest X-ray shows no pneumothorax, PCV is more than 40%, extubation is done. Adequate humidification of inspired air should be ensured. Nasal prone CPAP at the same pressure should be contained. Oral feeding should be stopped for 12–24 hours as feeds decrease PaO<sub>2</sub>. Careful aspiration of the mouth and oropharynx is done. Once the infant is extubated and is on nasal CPAP, CPAP can be discontinued gradually, 1–2 cmH<sub>2</sub>O at a time for a week or more.

## COMPLICATIONS

- Pneumothorax
- BPD
- IVH
- PDA
- Fluid overload
- PIF
- Laryngeal stenosis
- Neurological handicap
- Septicemia

CNS hemorrhage, IVH, and PDA represent significant clinical problems affecting the care of infants with RDS. Patent ductus arteriosus, subsequent congestive heart failure, and pulmonary edema further compromise respiratory function, decreasing pulmonary compliance and perhaps inactivating pulmonary surfactant.

Prompt diagnosis and medical or surgical treatment of PDA are indicated during the treatment of RDS.

Acute CNS hemorrhage is often associated with shock, pulmonary compromise and pulmonary hemorrhage. Fluctuations in respiratory status may contribute to IVH and can be minimized by careful attention to respiratory care and by judicious use of sedation.

Intravenous fluids and administration of oral feedings must be adjusted carefully during acute and convalescent care of infants with RDS. Excessive fluid administration impairs pulmonary function and increases the risk of PDA.

## PREVENTION

Neonatal RDS is associated with incomplete development of the lung at the time of birth. Thus,

premature delivery should be delayed, where possible. If this cannot be avoided, additional efforts should be made to accelerate lung maturation. Animal studies have shown that antenatal administration of glucocorticoids accelerates both structural and biochemical (surfactant) lung maturation.

Administration of betamethasone to women in premature labor at least 2 days before delivery significantly reduced the incidence of respiratory distress. Numerous studies following this pivotal publication have confirmed that antenatal glucocorticoids reduce mortality and perinatal morbidities such as RDS, IVH, and NEC. Treatment consists of two doses of 12 mg of betamethasone given intramuscularly 24 hours apart, or four doses of 6 mg of dexamethasone given intramuscularly 12 hours apart. The benefits of antenatal steroid typically begin at around 24 hours after initiation of therapy and lasts 7 days. Current guidelines recommend treatment with antenatal

glucocorticoids if preterm delivery is imminent between 24 and 34 weeks of gestation.

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## PRESENTING COMPLAINTS

A 10-year-old boy was brought with the complaints of:

- Obesity since 6 months
- Withdrawal behavior since 6 months
- Pessimistic attitude since 3 months

## History of Presenting Complaints

A 10-year-old boy was brought to hospital with problem of obesity. The boy was worried about his own obesity. That made him to develop withdrawal behavior. His psychosomatic symptoms started worrying his parents. Mother complained that he would remain alone. He was not showing much interest in playing along with his peers. Mother also told that he used to avoid any work which requires physical exercise. He started developing pessimistic attitude.

## Past History of the Patient

He was the elder sibling of consanguineous marriage. He was delivered at full term by normal vaginal delivery. The birth weight of the child was 3.5 kg. There was no significant postnatal event except normal physiological jaundice. He was

bottle-fed since birth and cereals and fruits were started when he was 6-month-old. His mother had no records of infancy but she told that he had been always with big body. His developmental milestones were normal. He had been completely immunized. Mother told that she never thought that his son ate excessively and never worried that he was overweight. A dietician assessed and calculated that his daily intake was about 3500 calories.

## EXAMINATION

The child was obese. He was moderately built. His anthropometric measurements included, the height was 135 cm (50th centile), the weight was 46 kg (>97th centile). He was tall and weight was out of proportion.

He was afebrile. Pulse rate was 100 per minute, the respiratory rate was 20 per minute. The blood pressure recorded was 110/80 mm Hg. There was no pallor, no lymphadenopathy, no cyanosis and no clubbing. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 14 g/dL
TLC	: 7,200 cells/cu mm
DLC	: P <sub>55</sub> L <sub>40</sub> E <sub>3</sub> M <sub>0</sub>
ESR	: 26 mm in the 1st hour
AEC	: 300 cells/dL
Urine examination	: Normal
X-ray chest	: Normal

## DISCUSSION

Obesity is the most common nutritional disorder of children. Here adipose tissue is enlarged out of proportion to other body organs. It is the term used when the weight exceeds 120% of standard weight. In practice simple observation of undressed child leaves little doubt about the diagnosis.

The body mass index (BMI) defined as  $wt/ht^2$  (in kg per m<sup>2</sup>) is most useful index. It correlates significantly with subcutaneous and total fat in

### CASE AT A GLANCE

#### Basic Findings

Height	: 135 cm (50th centile)
Weight	: 46 kg (>97th centile)
Temperature	: 37°C
Pulse rate	: 100 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 110/80 mm Hg

#### Positive Findings

##### History

- Overweight
- Psychosomatic symptoms

##### Examination

- Normal

##### Investigation

- Normal

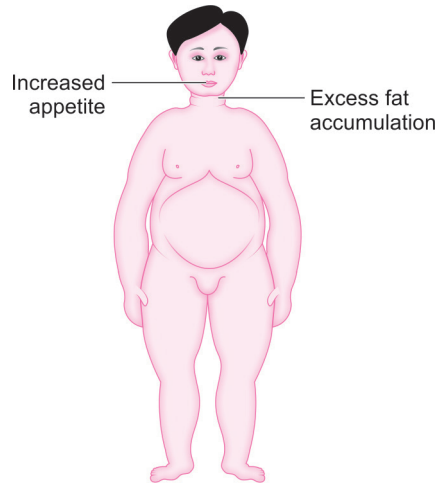
adolescents. The term overweight is used when BMI exceeds 95th percentile for that age and sex. Skin fold thickness above 85th percentile for age and sex also suggests obesity. It can be measured at triceps, midabdominal or subscapular sites.

The hypothalamus contains two important sets of neurons: anorexigenic (appetite suppressing) proopiomelanocortin (POMC) neurons and orexigenic (appetite promoting) neuropeptide Y (NPY) neurons. Hormones that are direct measures of the energy status of an individual (i.e., fasting or fed) can directly activate or suppress these neurons to bring the individual back to equilibrium. Insulin, glucose, leptin, lipids, and the gut-derived peptides cholecystokinin, amylin, peptide YY (PYY), glucagon-like peptide-1 (GLP-1), ghrelin, and gastric inhibitory peptide (GIP) all have actions within the brain to control food intake. For instance, after a meal, glucose levels rise along with insulin levels. Insulin can activate POMC neurons and inhibit NPY neurons, which promotes satiety and the cessation of eating. There is also evidence that the body will defend a higher body weight through decreased energy expenditure and/or increased hunger after weight loss. These pathways are highly complex and contribute to the difficulty in losing weight and maintaining weight loss in the obese individual.

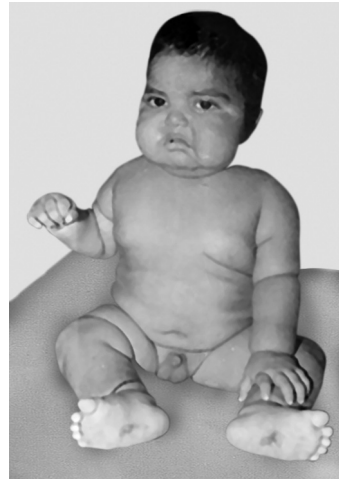
The most common method for clinically identifying a child as being overweight or obese relies on the definition for children using the BMI. BMI percentile is used and recommended most frequently because it is easy and inexpensive to obtain. This index is a reflection of weight for height. As a child grows, normal BMI values vary with age and sex, thus, a single absolute cutoff of BMI as a measure of obesity is not available in youth. Overweight for children is defined as a BMI at or above the 85th percentile but below the 95th percentile for the child's age and gender. Obesity is defined as BMI at or above the 95th percentile for the child's age and gender. Severe or extreme levels of pediatric obesity have also been defined using several different criteria. Extreme obesity has been reported as BMI at the 97th and 99th percentiles; at the 120th percentile above the 95th percentile; or as excess overweight calculated as  $100 \times (\text{BMI}/50\text{th percentile BMI for child age and gender})$ .

### CLINICAL FEATURES (FIG. 1)

Many times diagnosis is made from child's appearance. Obesity (**Fig. 2**) or overnutrition is generalized. Excessive accumulation of fat in the



**Fig. 1:** Clinical features.



**Fig. 2:** Obesity.

subcutaneous and other tissues can be quantitated by measuring skin fold thickness with skin fold calipers. It is mainly due to excessive intake of the food.

Genetic predisposition may also be present. Lack of activity may be responsible for obesity even though intake of food may not be unusual. It may result from increase in number or size of fat cells, adipocytes. Adipocytes appear to increase in number when caloric intake is increased.

Stocky children may have relatively large skeletal frames and have more than average amount of muscular tissue. Appetite may be influenced by various factors. These include psychogenic disturbances, hypothalamus, pituitary or other brain lesions. Some inherited syndromes

such as Laurence-Moon-Biedl, Prader-Willi and Cushing may also be responsible.

The adiposity in the mammary region of boy is often suggestive of breast development and an embarrassing feature. The obesity of the extremities is usually greater in the upper arm and thigh. The hands may be relatively small and fingers are tapering. Genu valgum is common. Psychological disturbance is also common.

Obese children carry a large body weight. This tires them more easily and further reduces physical activity. Clinical features of endocrine, hypothalamic or various cryptogenic syndrome are obvious. Traumatic inflammation, neoplastic lesion of hypothalamus and pituitary gland causes increased appetite and hence obesity.

Leptin is adipose tissue secreted hormone with receptors in hypothalamus. Plasma level of leptin correlates with body fat mass and are regulated by feeding, fasting, insulin and steroid.

Insulin decreases lipolysis and increased fat syntheses and uptake. Genetic studies have shown the relation between leptin, gene and obesity.

The obese respond to carbohydrate meal with increased insulin and decreased utilization of free fatty acids. Protein conservation is facilitated as the brain utilizes ketones for energy. If the obesity is initiated early, it is likely to persist. There is good evidence that fat children will become fat adult.

It can become evident at any age but most frequently it is seen in the first year, 5–6 years of age and during adolescence. The facial features often appear disproportionately fine. The abdomen is tender to be pendulous. White and purple striae are often present. The external genitalia of the boy is disproportionately small. Penis is often embedded in pubic fat.

Puberty may occur early, hence ultimate height of the person is less. The development of external genitalia is normal in majority of girls. Menarche is not usually delayed.

The extreme exogenous obesity produces severe cardiorespiratory distress in pulmonary, tidal and expiratory reserve volume. The manifestations include polycythemia, hypoxemia, cyanosis, cardiac enlargement and congestive cardiac failure.

Obesity may be exogenous and endogenous.

#### *Exogenous obesity*

- Constitutional
- Excessive food intake
- Decreased energy expenditure
- Fat cell hyperplasia

#### *Endogenous obesity*

- Genetic
  - Prader-Willi syndrome
  - Laurence-Moon-Biedl syndrome
- Hormonal
  - Hypothyroidism
  - Hypogonadism
  - Pseudohypoparathyroidism
  - Cushing's syndrome
- Hypothalamic
  - Obesity

Those with BMI > 85 percentile for the age should be investigated, if they have any of the following:

- Family history of cardiovascular complications of type II diabetes
- Rapid increase in obesity
- Hypertension

Blood sugar, serum cholesterol, lipid profile, CFT, skeletal maturity evaluation, hormonal test, i.e., urine free cortisol, FT<sub>4</sub> and TSH, testosterone, estradiol and gonadotropin assay as suggested by clinical examination.

### CLINICAL EVALUATION

The evaluation of obesity has three main purposes: (1) to exclude underlying pathology; (2) to evaluate potential comorbidities of obesity, and (3) to identify underlying behavioral and environmental variables that can be targeted to improve the child's weight status.

Possible identifiable causes of obesity include iatrogenic, endocrine, or genetic conditions. Iatrogenic causes include glucocorticoids, appetite stimulants, certain antidepressants, antipsychotics, oral hypoglycemic agents, or surgical injury to the hypothalamus. Endocrine causes, such as hypothyroidism or Cushing syndrome, are almost always accompanied by decreased linear growth. Very early-onset obesity, developmental delays, and/or impaired learning may be signs of a genetic disorder. Melanocortin-4 receptor mutations are the most common genetic form of obesity and are associated with early-onset obesity and a strong family history of severe obesity. Prader-Willi syndrome (loss of imprinted genes on 15q11-q13) is the most common syndromic form of obesity. Given the rarity of genetic syndromes in causing obesity in the general population, further discussion is outside the scope of this chapter. A good history and physical exam are often sufficient to identify whether there is any concern for an underlying genetic or hormonal etiology of obesity.



**GENERAL FEATURES**

- Overweight
- Behavioral problems

**DIFFERENTIAL DIAGNOSIS**

- Overeating
- Endocrine disorders such as hypothyroidism, pseudohypoparathyroidism and Cushing's syndrome
- Fröhlich's syndrome (adipose genital dysmorphism)
- Prader-Willi syndrome—obesity starts from late infancy, upper slanting of palpable fissure, hypogonadism, mental retardation, strabismus and short stature.

Initial laboratory screening tests may include fasting blood sugar and/or hemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and a lipid panel, to assess for metabolic dysfunction. Further laboratory evaluation for polycystic ovary syndrome or hypertension should be performed as needed. Unless the history and physical exam suggest concern for other conditions, such as hypothyroidism, additional lab screening is not necessary. Although the initial screening (e.g., thyroid-stimulating hormone [TSH]) tests for the evaluation of obesity are consistent across guidelines, there is no clear consensus on when subsequent screening should be performed.

**TREATMENT**

These children should be encouraged to take foods rich with fiber but low caloric content before they take their main meals. A full stomach gives a feeling of satisfaction and therefore the intake is reduced. Greater physical activity should be encouraged. Attempts should be made to reduce the weight gradually rather than promptly. Use of drugs to reduce appetite should be discouraged. Surgical methods are not recommended in children. It is considered only when obesity is life threatening.

Caloric intake should be reduced. Children should be encouraged to take high fiber food, but low caloric contact. General physical activity should be encouraged. Sometime child may require psychological support and encouragement. Use of drugs to reduce appetite should be discouraged.

**Pharmacotherapy**

Two medications (orlistat, sibutramine), have been tested in randomized control trials. Orlistat is a gastrointestinal lipase inhibitor, and sibutramine

is a serotonin and norepinephrine reuptake inhibitor. Combined with behavioral interventions, these two drugs resulted in small to moderate short-term weight loss in obese adolescents (BMI reduction of 2.6 kg/m more for sibutramine, 0.85 kg/m more for orlistat compared to placebo). Potential side effects include increase in heart rate and blood pressure with sibutramine and gastrointestinal side effects with orlistat that can be prohibitive for continued use. There have also been reports of liver injury, cholelithiasis, and pancreatitis with orlistat. Data on weight maintenance after interruption of therapy are not available. Only orlistat is FDA approved for use in children and adolescents 12 years and older. Sibutramine was voluntarily withdrawn in 2010 because of an association with increased incidence of cardiovascular events among adults at high risk for cardiovascular disease. Metformin, an insulin sensitizer, is approved for the treatment of type 2 diabetes in children 10 years of age and older. It can result in modest weight loss among children with type 2 diabetes.

**Surgery**

Bariatric surgery is a consideration in the setting of severe obesity in adolescents, particularly if associated with comorbidities. However experts recommend that adolescents should be considered for bariatric surgery only if they are severely obese (BMI > 40 kg/m) and have serious medical comorbidities associated with their obesity, have reached Tanner stage of 4 or greater to ensure skeletal maturity, have demonstrated commitment to lifestyle change, have tailored at least 6 months of a structured weight loss program, and have a stable psychosocial environment. It may also be appropriate with BMI > 35 kg/m if associated with severe comorbidities such as type 2 diabetes mellitus, moderate to severe sleep apnea, or pseudotumor cerebri. These factors are best assessed in a pediatric tertiary care center in the context of a multidisciplinary program.

Different surgical modalities, including restrictive or malabsorptive procedures, or a combination, can be employed. They include the Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion, adjustable gastric banding (AGB), and the vertical sleeve gastrectomy (VSG). Bariatric surgery can lead to massive reductions in body weight, BMI, and fat mass, with reports of 50–60% of excess weight loss in the first year, with absolute BMI reduction or about 30%. This reduction is associated with marked improvement or resolution of

obesity-related comorbidities and improvement in mental health and quality of life.

Side effects include potential serious surgical complications, including pneumonia, deep venous thrombosis, pulmonary embolus, gastrointestinal hemorrhage, anastomotic obstruction, wound infections, risk for cholelithiasis, and even death.

Postoperatively, nutritional status should be closely monitored and supplementation provided to avoid macronutrient (mostly protein) and micronutrient (fat-soluble vitamins, iron, and calcium) deficiencies, which are particularly concerning in the growing adolescent. Bariatric surgery and continued management of adolescents should be done only by a multidisciplinary team with pediatric expertise.

## SUMMARY

Obesity remains a common pediatric medical condition that most clinicians will have to address among their patients due to the impact that obesity has on many disease processes and conditions.

In pediatric primary care, overweight and obesity should be screened for and depending on the weight status of the child, either obesity prevention or weight management should be addressed during well-child and/or follow-up visits. Clinicians should help advocate for children both in their clinical practice and in their community for healthy eating and physical activity behaviors, along with health-promoting environments for children.

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# Protein-energy Malnutrition

## PRESENTING COMPLAINTS

An 18-month-old boy was brought with the complaints of:

- Irritability since 6 months
- Generalized swelling since 4 months
- Skin lesion since 1 month
- Loose motion since 15 days

## History of Presenting Complaints

An 18-month-old boy was brought to the pediatric outpatient department with history of irritability, generalized swelling and skin changes. His mother complained that her son was more irritable and he was not taking feeds regularly. His food intake was very less. Mother told that he used to sit quietly in one place and was not playful. His mother also told that his son was getting repeated episodes of loose motions. She noticed that the child developed the swelling of the limbs and face.

### CASE AT A GLANCE

#### Basic Findings

Height	: 78 cm (25th centile)
Weight	: 8 kg (below 3rd centile)
Temperature	: 37°C
Pulse rate	: 110 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 60/40 mm Hg

#### Positive Findings

##### History

- Irritability
- Generalized swelling
- Skin changes
- Poor appetite

##### Examination

- Irritability
- Generalized edema
- Skin changes
- Hair changes

##### Investigation

- Anemia
- Abnormal LFT
- ESR raise

The swelling was gradually increasing. She told about presence of skin lesions at the elbow. Itching and desquamation were present.

## Past History of the Patient

He was the third sibling of nonconsanguineous marriage. He was born at full term by normal vaginal delivery. The baby cried immediately after the delivery. The birth weight was 2.5 kg. He started to take breastfeeds regularly. He was on breastfeed for first 3 months. Later weaning started. He was on family food by 1 year. His developmental milestones were delayed. He had been completely immunized.

## EXAMINATION

On examination, the child was moderately built and poorly nourished. He was irritable and crying. Anthropometric measurements included, the height was 78 cm (25th centile), the weight was 8 kg (below 3rd centile). The head circumference was 45 cm.

He was afebrile, the heart rate was 110 per minute, the respiratory rate was 26 per minute. The blood pressure recorded was 60/40 mm Hg.

There was pallor. Generalized edema was present. There was no cyanosis and no clubbing. Skin changes included the hyperpigmented areas in flexor place on ventral surface. Desquamation was present. The hair changes included the sparse lusterless, easily pluckable hair. The texture of the hair was coarse. Muscles were thin and weak.

Respiratory system revealed the presence of bilateral coarse crepitation at the base. Per abdomen examination revealed the presence of hepatomegaly measuring about three centimeters below the costal margin. Cardiovascular system and central nervous system were normal.

## INVESTIGATION

Hemoglobin	: 8 g/dL
TLC	: 7,600 cells/cu mm
ESR	: 40 mm in the 1st hour

Blood glucose	: 60 mg/dL
Serum potassium	: 3 mEq/dL
Serum magnesium	: 2 mEq/dL
Serum bilirubin	: 1.2 mg/dL
Alkaline phosphatase	: 600 U/L
SGOT	: 150 IU/L
SGPT	: 70 IU/L
Peripheral blood smear	: Microcytic hypochromic anemia
X-ray chest	: Suggestive of pneumonia

## DISCUSSION

The clinical state is mainly because of insufficient protein. It may also be because of impaired absorption of protein as in chronic diarrhea or chronic liver disorders. The growing child must maintain a positive nitrogen balance. Deficiency of calories and other nutrients will complicate the clinical and chemical patterns.

Acute malnutrition results in wasting (decrease in weight for height) and occur when food consumption is suddenly severely reduced. Chronic under nutrition occurs when long-term food consumption is insufficient to cover the requirements for daily energy expenditure. It results in stunting (decrease in height for age).

## ETIOLOGY

*Large families:* Rapid succession of pregnancies adversely affects the nutritional status of mother. Their fetuses tend to be small and this is reflected in high incidence of low birth weight.

*Feeding habits:* A child is more likely to have *protein-energy malnutrition (PEM)* if exclusive breast feeding is not given for first 4–6 months, lactation fails, breast milk supply is not sufficient and introduction of solid energy dense and protein-rich complementary food is delayed.

*Infections:* Infections such as malaria, whooping cough, tuberculosis and measles precipitate acute malnutrition and aggravate the existing nutritional deficit. Recurrent attacks of diarrhea in preschool children are a major contributory factor in etiology. Malnutrition may adversely affect the immune status and make the malnourished individuals more vulnerable to infections. This sets up a vicious cycle of malnutrition infection malnutrition.

## PATHOPHYSIOLOGY

When a child's intake is insufficient to meet daily needs, physiologic and metabolic changes take place in an orderly progression to conserve energy

and prolong life. This process is called reductive adaptation. Fat stores are mobilized to provide energy. Later protein in muscle, skin, and the gastrointestinal tract is mobilized. Energy is conserved by reducing physical activity and growth, reducing basal metabolism and the functional reserve of organs and by reducing inflammatory and immune responses. These changes have important consequences:

- The liver makes glucose less readily, making the child more prone to hypoglycemia. It produces less albumin, transferrin, and other transport proteins. It is less able to cope with excess dietary protein and to excrete toxins.
- Heat production is less, making the child more vulnerable to hypothermia.
- The kidneys are less able to excrete excess fluid and sodium, and fluid easily accumulates in the circulation, increasing the risk of fluid overload.
- The heart is smaller and weaker and has a reduced output, and fluid overload readily leads to death from cardiac failure.
- Sodium builds up inside cells due to leaky cell membranes and reduced activity of the sodium/potassium pump, leading to excess body sodium, fluid retention, and edema.
- Potassium leaks out of cells and is excreted in urine, contributing to electrolyte imbalance, fluid retention, edema, and anorexia.
- Loss of muscle protein is accompanied by loss of potassium, magnesium, zinc, and copper.
- The gut produces less gastric acid and enzymes, Motility is reduced, and bacteria may colonize the stomach and small intestine, damaging the mucosa and deconjugating bile salts. Digestion and absorption are impaired.
- Cell replication and repair are reduced, increasing the risk of bacterial translocation through the gut mucosa.
- Immune function is impaired, especially cell-mediated immunity. The usual responses to infection may be absent, even in severe illness, increasing the risk of undiagnosed infection.
- Red cell mass is reduced, releasing iron which requires glucose and amino acids to be converted to ferritin, increasing the risk of hypoglycemia and amino acid imbalances. If conversion to ferritin is incomplete, unbound iron promotes pathogen growth and formation of free radicals.
- Micronutrient deficiencies limit the body's ability to deactivate free radicals, which cause cell damage. Edema and hair/skin changes are outward signs of cell damage.

When prescribing treatment it is essential to take these changes in function into account, otherwise organs and systems will be overwhelmed and death will rapidly ensue.

## CLASSIFICATION

The PEM may be classified according to the severity, course and the relative contributions of energy or protein deficit. Severity classifications are based on anthropometric measurements, mainly weight and height. Accordingly several classifications are suggested.

- **Indian Academy of Pediatrics (IAP) classification:** This is an IAP classification. Weight of more than 80% of expected for age is taken as normal. Grades of malnutrition are grade I (71–80%), II (61–70%), III (51–60%) and IV (<50%) weight of expected for that age.
- **Welcome Trust classification:** This is based on deficit in body weight for age and presence or absence of edema. Children weighing between 60 and 80% of their expected weight for age with edema are classified as kwashiorkor. Those weighing between 60 and 80% of expected without edema are known as having undernutrition. Those without edema and weighing less than 60% of their expected weight for age are considered to be having marasmus. Children with edema and body weight less than 60% of expected are labeled as having marasmic kwashiorkor.
- **WHO classification:** This is based on all four parameters, i.e., weight for age, height for age, weight for height and edema. WHO recommends three terms, i.e., stunting, underweight and wasting for assessing the magnitude of malnutrition in under five children.

## CLINICAL FEATURES (FIG. 1)

Malnutrition causes a variety of metabolic disturbances. Resistance to infections is decreased, gastrointestinal functions are disturbed and learning ability is adversely affected. The growth of children is retarded and there is high morbidity and mortality among malnourished individuals.

### Nutritional Marasmus and Kwashiorkor

The two extreme forms of malnutrition account only for a small proportion of malnourished children. A much larger number of subjects suffer from mild to moderate nutritional deficit.

If the food deficit persists for a longer period, the malnourished subject conserves his energy by curtailing physical activity. Moderately malnourished

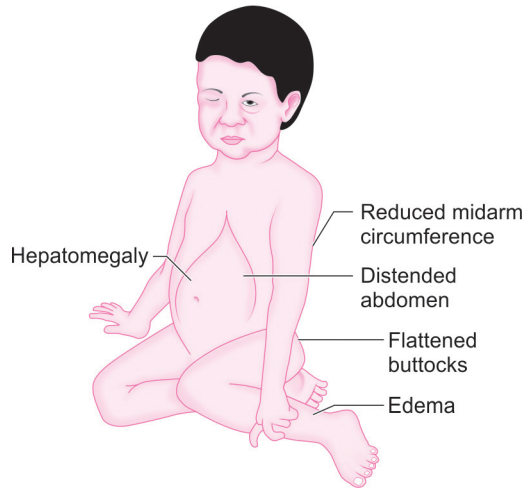


Fig. 1: Clinical features.

children appear slower and less energetic. If the nutrition deficit continues longer, growth of the child is affected. Growth lag is more pronounced in weight than the length. With prolonged deprivation, height is also stunted. Head circumference is not reduced significantly. Chest circumference normally exceeds the head circumference by the age of 1 year, but it may not do so till much later in malnourished children.

The weight of the child is reduced and appears disproportionate with long body, thin limbs and unduly large head. Buttocks are flattened with wrinkling of skin over the front of thighs. The scapulae have become winged. Abdominal wall is thin and therefore abdomen appears distended. As the nutritional deficit exaggerates with the onset of infections, the child may become marasmic or develop kwashiorkor.

### Marasmus

A marasmic subject is markedly emaciated. The body weight is less than 60% of the expected weight for the age. The fat in the adipose tissues is severely depleted because it is used up for providing energy. The contour of atrophic muscles is evident under the thin and wrinkled skin. Loose folds of skin are prominent over the gluteal and the inner side of thigh. The buccal pad of fat is preserved till the malnutrition becomes extreme.

A higher proportion of saturated fatty acids is stored there and the saturated fat is the last to be depleted. The skin appears dry and inelastic and is prone to be infected. The hair is hypopigmented.

The abdomen is distended due to wasting and hypotonia of abdominal wall muscles. The midarm



circumference is reduced. The bony points appear unduly prominent due to emaciation. The baby appears alert, but is often irritable. Marasmic children may show voracious appetite.

### *Kwashiorkor*

Markedly retarded growth, psychomotor changes and edema of dependent parts are three essential clinical features of kwashiorkor. The edema starts in the lower extremities and later involves upper limbs and the face. Muscles of the upper limbs are wasted, but the lower extremities appear swollen. The face appears moon-shaped and puffy. The trunk is affected to a lesser extent. Debilitating illnesses such as measles or diarrhea can precipitate edema. With the onset of kwashiorkor, the previously peevish and irritable undernourished child becomes lethargic, listless and apathetic. The child takes little interest in the environment and does not play with his toys.

The kwashiorkor patient appears miserable and resents examination by the physician. Appetite is impaired and it is difficult to feed him orally.

The hair is thin, dry, brittle and devoid of its normal sheen. The length of the hair growing during the period of nutritional deprivation appears reddish brown. During the phases of better nutrition, the growing part of the hair gets appropriately pigmented. This gives appearance of alternate bands of hypopigmented and normally pigmented hair (flag sign) (**Fig. 2**). These children often suffer from recurrent episodes of diarrhea, respiratory and skin infections.

#### ESSENTIAL DIAGNOSTIC POINTS

- Growth retardation
- Anorexia
- Generalized edema
- Skin changes
- Hepatomegaly
- Electrolyte disturbances
- Hair changes

The liver is enlarged with rounded lower margin and soft consistency in about one-third of cases.

Large areas of skin may show erythema or hyperpigmentation. The skin becomes dry and hyperkeratotic. The epidermis peels off in large scales, exposing tender raw area underneath. It gives appearance of old paint flaking off the surface of the wood. The underlying raw skin is easily infected. The skin lesions are marked in areas of the body, most exposed to continuous pressure and irritation. Petechiae or ecchymosis appear in severe cases.

As the nutritional deficiencies are generally multiple, anemia due to iron, protein, vitamin B or folate-deficiency is often associated. Deficiencies of vitamin B complex factors, especially ariboflavinosis are common (**Figs. 3A and B**). Keratomalacia due to vitamin A deficiency is reported in 10–20% of patients with kwashiorkor. Associated scorbutic changes manifest as bleeding gums, subperiosteal hemorrhage or even ecchymotic spots. Subclinical ascorbic acid deficiency is frequent in malnutrition. Rickets due to vitamin D deficiency is present in only 5% cases, though almost all cases would have subclinical vitamins D and A deficiency.



**Fig. 2:** Flag sign.



**Figs. 3A and B:** (A) Glossitis; (B) Oral thrush.  
(For color version see Plate 7)

**Severe acute malnutrition (SAM):** Children will mix of marasmus and kwashiorkor. They will have any of the following three criterias:

1. Weight for height below -3 standard deviation
2. Presence of bipedal edema
3. Midarm circumference below 11.5 cm.

#### GENERAL FEATURES

- Placid, slow, less active
- Wrinkling of the skin over front of thigh
- Irritable
- Edema
- Thin, dry, brittle hair
- Chronic diarrhea
- Hypopigmentation
- Hyperpigmentation

### CLINICAL SIGNS OF MALNUTRITION

#### Signs

- Moon face (kwashiorkor), simian fades (marasmus)
- Dry eyes, pale conjunctiva, Bitot spots (vitamin A), periorbital edema
- Angular stomatitis, cheilitis, glossitis, spongy bleeding gums (vitamin C), parotid enlargement
- Enamel mottling, delayed eruption
- Dull, sparse, brittle hair, hypopigmentation, flag sign (alternating bands of light and normal color), broomstick eyelashes, alopecia
- Loose and wrinkled (marasmus), shiny and edematous (kwashiorkor), dry, follicular hyperkeratosis, patchy hyper- and hypopigmentation (crazy paving or flaky paint dermatoses), erosions, poor wound healing
- Koilonychia, thin and soft nail plates, fissures, or ridge
- Muscle wasting, particularly buttocks and thighs; Chvostek or Trousseau sign (hypocalcemia)
- Deformities, usually as a result of calcium, vitamin D, or vitamin C deficiencies
- *Distended:* Hepatomegaly with fatty liver; ascites may be present
- Bradycardia, hypotension, reduced cardiac output, small vessel vasculopathy
- Global developmental delay, loss of knee and ankle reflexes, impaired memory
- Pallor, petechiae, bleeding diathesis
- Lethargic, apathetic, irritable on handling

### DIFFERENTIAL DIAGNOSIS

- Nephrotic syndrome
- Angioneurotic edema
- Chronic diarrhea

- Malnutrition
- Infestation
- Malabsorption syndrome

### TREATMENT

#### Management

The management of PEM depends on nutritional status, degree of hypermetabolism, expected duration of illness and associated complications. The goals are to minimize weight loss, to maintain body mass and to encourage body mass repletion or growth.

The management consists of three phases:

1. *Resuscitation:* Lasts for 6–24 hours
2. *Acute phase:* 1 day to 1 week/+
3. *Rehabilitation:* Through 2nd and 3rd weeks to 6 weeks. The period of phases especially the first two phases may vary depending on the condition of the child when brought for medical attention.

WHO has suggested guidelines for the inpatient treatment of severely malnourished children, the general principles are as follows.

#### Dehydration

Assessment of dehydration is difficult due to wasting and edema. However, dry oral mucosa, acidotic breathing, oliguria, absence of tears and peripheral circulatory failure are most reliable signs.

The amount of fluid and sodium should not exceed 75% of the allowances calculated on the basis of weight and age (because of reduced capacity to excrete water and inability to excrete sodium).

Additional fluid can be given if needed. Fluid deficit and maintenance fluids are calculated. Deficit fluid volume is replaced by 5% dextrose in N/2 saline in 6–8 hours, and maintenance fluid volume is given as isolyte P over 16 hours.

If child has shock, Ringer's lactate 30 mL/kg or 20 mL/kg of 0.45% saline (1/2) in 5% dextrose is given in hour, then 70 mL/kg of Ringer's lactate or 10 mL/kg in 1 hour of glucose saline for two hours. If shock does not improve then 10 mL/kg of plasma is infused. Potassium is added in infusion in dosage of 2–3 mEq/kg (maximum dose 40 mEq/L), when a flow of urine is observed.

In mild dehydration, ORS (oral rehydration salt—WHO—sodium chloride 3.5 g, potassium chloride 1.5 g, sodium citrate 2.9 g, glucose 20 g) should be given. Severely malnourished children with dehydration may not tolerate this high sodium low potassium ORS.

Ongoing loss of water in stool is provided at 10 mL/kg/stool. Once child is stable and he is able to accept oral feeds, milk-based therapeutic nutrition is started.

The indications for hospitalization are hypothermia, infection, fluid and electrolyte imbalance, convulsions, unconsciousness, xerophthalmia, severe dermatosis, extreme weight deficit, bleeding, marked hepatomegaly, jaundice, purpura raised liver enzymes, severe anemia and cardiac failure, persistent vomiting, severe anorexia, distended tender abdomen and age less than 1 year.

### *Correction of Electrolyte Imbalance*

All severely malnourished child usually have potassium and magnesium deficiencies which may take at least 2 weeks to correct. It is corrected by giving extra potassium 2–4 mmol/kg/day, extra magnesium 0.3–0.6 mmol/kg/day, restricting the salt. When rehydrating low sodium rehydration fluid is given. The extra potassium and magnesium can be prepared in a liquid form and added directly to feeds during preparation.

*Hypothermia:* It is common in marasmus and is usually a manifestation of infection, hypoglycemia or severe energy deficit. Child is kept in warm room well-covered close to mother and is given frequent feeds and antibiotics for infection. If the axillary temperature is  $<35^{\circ}\text{C}$  take rectal temperature using a low reading thermometer, if below  $35.5^{\circ}\text{C}$  ( $95^{\circ}\text{F}$ ) feed straight away (or start rehydration if needed).

*Hypoglycemia:* It is again more common in marasmus with hypothermia, septicemia and coma. It requires 10% glucose 1–2 mL/kg in bolus followed by 10% dextrose in N/5 saline in maintenance dose for 24 hours. Antibiotics are given and continue 2 hourly feeds, day and night. As hypoglycemia and hypothermia usually occur together and are signs of infection, check for hypoglycemia whenever hypothermia is found. Frequent feeding is important in both conditions.

*Infection:* Diagnosis of fulminant infection is made by high index of suspicion or in the presence of hypothermia, apathy, convulsion or coma. Antimicrobials (broad spectrum) are started immediately while awaiting culture reports. Gastric aspirate examination and culture, X-ray chest and Mantoux test are done to diagnose pulmonary tuberculosis. Blood film for malaria may be required.

If the child has no complications, cotrimoxazole 5 mL orally twice daily for 5 days (2.5 mL if weight  $<4$  kg) (5 mL is equivalent to 40 mg TMF + 200 mg SMX) or if the child is severely ill, has complications

give intravenous ampicillin (50 mg/kg/6 hourly for 2 days) then oral amoxicillin for 5 days or continue ampicillin for 5 days. Add gentamicin 7.5 mg/kg IM/IV for once.

If no improvement within 48 hours add chloramphenicol 25 mg/kg/IM/IV for 5 days or appropriate antibiotic, if specific infections are identified. If anorexia persists after 5 days course, antibiotics are continued for full 10 days. If no/poor response, reassess the child fully. Some experts routinely give metronidazole 7.5 mg 8 hourly for 7 days to hasten intestinal repair of mucosa and reduce the risk of potential anaerobic infection.

*HIV/AIDS:* In children with HIV/AIDS, good recovery from malnutrition is possible though it may take longer and treatment failures may be common. Lactose intolerance occurs in severe HIV related chronic diarrhea. Treatment should be same as for HIV negative children.

*Anemia:* If hemoglobin is less than 5 g/dL, small packed cells transfusion (5–10 mL/kg) is given. In children with impending cardiac failure, partial exchange transfusion (10–20 mL/kg) may be quite beneficial. Whole blood transfusion (10 mL/kg) has been recommended for severely ill-malnourished children. Iron supplementation for anemia is withheld for first 1–2 weeks to allow transferring regeneration and to permit resolution of infection.

*Xerophthalmia:* Vitamin A, 1 lac units aqueous preparation should be given to all severely malnourished children on days 1, 2 and 28th in children above 1 year of age or more than 10 kg weight. In infants below 1 year or weight less than 10 kg,  $\frac{1}{2}$  of the above dose is given. If the infant is between 0 and 6 months 50000 units are given.

*Congestive heart failure:* It is most common after 3 days of acute phase usually in kwashiorkor. Oxygen inhalation and diuretics are helpful.

*Hypocalcemia:* Requires correction by calcium gluconate IV 1–2 mL/kg or calcium lactate powder 3 g/day orally.

*Zinc deficiency:* Role of zinc supplementation is controversial. Dose of zinc is 2 mg/kg/day.

*Other vitamins:* Appropriate vitamins should be supplied with 10 mL, MVI-dose is 1–2 mL daily in drip and later orally plus vitamin K 1–5 mg weekly.

*Copper, chromium and manganese deficiency:* Dose of copper is 20  $\mu\text{g/kg/day}$  that of chromium is 0.2 g/kg/day and manganese is 10  $\mu\text{g/kg/day}$ .

Although the phases of resuscitation and acute phases are divided separately, quite often the medical treatment started during the phase

of resuscitation continues into acute phase. The acute phase also may be prolonged to 2–3 weeks instead of 1 week as suggested.

#### LABORATORY SALIENT FINDINGS

- Anemia
- Hypoglycemia
- Hypocalcemia
- Hypomagnesemia
- Altered LFT
- Septic screen

## Dietary Management of Severe PEM

### Initial Phase

In the initial stabilization phase a cautious approach is required because of the child's fragile physiological state and reduced homeostatic capacity. Feeding should be started as soon as possible after admission and should be designed to provide just sufficient energy protein to maintain physiological processes.

It is for mild to moderate PEM and for those uncomplicated severe PEM who have fairly good appetite, normal body temperature, who are conscious and active and without evidence of serious infection. These children are managed at home by parents under observation and supervision.

The main goal of treatment is to provide adequate calories for dual purpose, to replace losses and to build-up nutrition and to promote growth. Caution must be taken to gradually build-up the calories and proteins. The energy recommended is 120–150 kcal/day and protein 2–3 g/kg/day of high biological value. Both of these should be based on locally available and affordable food sources, commonly consumed by the family.

Frequent small feeds with calories and proteins distributed proportionately are encouraged rather than 1 or 2 major bulky meals. Parents are educated about hygienic way of preparation and handling of food, use of safe and clean drinking water and importance of personal hygiene.

The regime recommended is one that provides near maintenance requirement, i.e., approximately 80 cal/kg/day and 0.7 g protein/day with the calculation being based on actual rather than expected weights. The second rule is to offer small amount of feeds of low osmolarity and low lactose at frequent intervals to avoid the incidence of vomiting, hypoglycemia and hypothermia. The intake can be gradually stepped up so that by the end of 1st week the child is able to take approximately 100 cal/kg/day and 1 g protein/kg/day. Some authorities suggest 100 kcal/kg/day and 1–1.5 g of proteins/kg/day.

Some basic advice is also given, for management of diarrhea by oral rehydration solution (ORS), immediate attention for treatment of common infestations and infections and appropriate management of anemia by oral iron and folic acid supplements and associated vitamin deficiencies.

To promote growth, zinc supplements are given when positive nutrition balance starts occurring and child manifests with increase in weight gain.

If the child is breastfed, continue to breast-feed but give starter formula (milk-based formulas containing 75 kcal/100 mL (0.9 g protein/100 mL) which will be satisfactory for most children. Very weak children may be fed by spoon, dropper or syringe. A recommended schedule in which volume is gradually increased and feeding frequency gradually decreased is:

Days	Frequency	Vol/kg/feed	Vol/kg/day
1–2	2 hourly	11 mL	130 mL
3–5	3 hourly	16 mL	130 mL
6–7+	4 hourly	22 mL	130 mL

For children with a good appetite and no edema this schedule can be completed in 2–3 days (e.g., 24 hours at each level).

Severely malnourished children often have refusal to feed and hence “forced feeding” by intragastric tube has to be done. Milk is the most common and nutritional liquid food and is also well tolerated except by children with secondary disaccharide (lactose) intolerance. Fluid volume is usually calculated approximately 130 mL/kg/day. This may be divided into 2 hourly feeds in the 1st week and 3 hourly thereafter, the calorie content of milk can be increased by adding oil as follows:

#### COMPOSITION OF ENRICHED MILK

Component	Energy (cal)	Protein (g)
Cow's milk (300 mL)	198	9.6
Sugar (85 g)	340	–
Vegetable oil (30 g)	270	–
Total	808	9.6

The amount of water added to this formulation would depend on the desired concentration of calories and proteins required and state of hydration of the individual patient since milk is the only fluid offered to the child. If the volume is made up of 1000 mL then 120 mL/kg/day and 1.1 g protein/kg/day. Coconut oil is the recommended oil as it is supposed to provide medium chain triglyceride (MCT); other oils are equally effective



besides coconut oil is not culturally used by all communities for feeding. Dietary LC-PUFA (long chain polyunsaturated fatty acids) have been known to improve intestinal repair in severe protein energy malnutrition, therefore its quantitative and qualitative supply should be considered.

The WHO has recommended milk-based formulas containing 75 cal/100 mL and 0.9 g protein/100 mL in the initial feeding schedule and then gradually increasing to supply 100 and 135 calories/100 mL of feed respectively for catch-up growth. These formulas are mainly based on the use of dried skimmed milk or dried whole milk and the use of these formulas is limited because of the economic constraints of the less advantaged communities of India where the problem of PEM is most common.

### *Phase of High Energy Feeding*

After the child passes through the initial phase and shows signs of improvement, tolerates the prescribed diet, one can then gradually increase the calorie intake to approximately 150–180 cal/kg/day. The amount of milk could be gradually decreased and the intake of semisolid/solids increased. The protein intake recommended during phase is in the range of 1.5–2 g/kg/day.

### **Therapeutic Diet**

Therapeutic diet should provide 150 kcal/kg/day for moderately undernourished and about 200 kcal/kg/day for severely malnourished children. About 10–15% of total calories should be obtained from proteins. A protein intake of 3 g/kg/day is sufficient. Milk is most frequent source of protein used in therapeutic diets.

As a general rule, the diet prescribed for the child should be such, which the family can afford to provide for the baby within its limited income, can be easily cooked at home, does not perish easily, is culturally acceptable and easily available in the local market. Expensive prestige foods may not necessarily be the most nutritious foods. Routine advice for giving fruit and eggs, etc., should be made only after due consideration of the family's economic constraints.

Milk-based diets may not be tolerated by some malnourished infants in the first few days due to transient lactose intolerance. If tolerated, milk-based diets are most suitable at the beginning of the treatment. If dried skimmed milk powder is used for reconstituting the milk, sugar and oil should be added to provide extra calories.

It is necessary to introduce semisolid diet with high calories and protein content, a week or fortnight after the start of the therapy. Extreme apathy and disinclination to eat make the treatment of kwashiorkor a trying experience. Feeding through a nasogastric tube for a few days' results in a dramatic change in the behavior of the patient, who then starts accepting oral feeds after a few days.

Every child should receive following intervention:

- Antibiotic therapy
- Dose of vitamin A—100,000 units (Xerophthalmia, Bitot's spots or keratomalacia)
- Albendazole single dose

### **ASSESSMENT OF RECOVERY AND FOLLOW-UP**

Recovery can be assessed by:

- Improvement of general condition, alertness and smile.
- Return of appetite.
- Gain in weight 50–70 g/day.
- Disappearance of edema (7–10 days) and hepatomegaly.
- Rise in serum albumin over the first 2 weeks of therapy.

The measure of efficacy of treatment of mild to moderate malnutrition is weight gain. Recovery is complete when the child reaches his or her standard weight which usually takes 6–8 weeks. Follow-up of such children is essential because, mortality rates of 10–30% have been reported after discharge from hospital. Continued supervision is necessary, till the expected weight for height has been achieved.

### **PROGNOSIS**

Mortality rates in severe PEM vary between 10 and 30%. The causes of deaths are same which determine hospitalization. Long-term sequelae of PEM are irreversible stunting and mental impairment.

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## PRESENTING COMPLAINTS

An 18-month-old boy was brought with the complaints of:

- Bow legs since 1 week
- Vomiting and loose motion since 15 days
- Abnormal walking since 1 week

## History of Presenting Complaints

An 18-month-old boy was brought to the pediatric outpatient department with history of abnormal walking. Mother told that his son's walking stature was different from other. She describes that it was just like waddling gait. She had also expressed the bow legs in his son. Change in walking style had changed or worsened after the recent acute gastroenteritis.

### CASE AT A GLANCE

#### Basic Findings

Height	: 80 cm (50th centile)
Weight	: 11 kg (60th centile)
Temperature	: 38°C
Pulse rate	: 106 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Abnormal walking
- Bow legs
- Delayed motor milestones

##### Examination

- Febrile
- Moderate dehydration
- Bow legs
- Double malleoli
- Abdominal distension

##### Investigation

- Microcytic hypochromic anemia
- Anemia
- Hypocalcemia
- Hypophosphatemia
- Increased alkaline phosphatase

## Past History of the Patient

He was the only sibling of nonconsanguineous marriage. He was born at full term by vaginal delivery. He cried immediately after the delivery. There was no significant postnatal event. He was exclusively on breast milk for 4 months. Weaning started later with cereals and fruits. He was on family food by 15 months. His motor developmental milestones were slightly delayed. He had been completely immunized.

## EXAMINATION

On examination, he was looking pale, and signs of moderate dehydration were present. He was moderately built and moderately nourished. Anthropometric measurements included, the height was 80 cm (50th centile), the weight was 11 kg (60th centile).

He was febrile, the pulse rate was 106 per minute, the respiratory rate was 26 per minute. The blood pressure recorded was 70/50 mm Hg. There was pallor, no lymphadenopathy, and no edema.

Anterior fontanelle was large and not closed. The wrist and knees were swollen. Bow legs were evident. Power in the lower limbs was less and finding very difficult to stand for long time. Double medial malleoli were present.

Respiratory system revealed presence of crepitations. Per abdomen examination showed the abdominal distension. There was no organomegaly.

## INVESTIGATION

Hemoglobin	: 8 g/dL
TLC	: 13,600 cells/cu mm
Platelet count	: 5,00,000 cells/cu mm
Serum calcium	: 2.5 mmol/L (Normal range: 2.2–2.7 mmol/L)
Serum phosphorus	: 0.8 mmol/L (Normal range: 1.25–2.1 mmol/L)

Alkaline phosphatase	: 500 U/L (Normal range: 30–120 U/L)
Peripheral blood smear	: Microcytic hypochromic anemia
X-ray of long bone	: Showed the cupping and flaring of the ends of the bone

## DISCUSSION

In general, baby had slightly delayed gross motor milestones. Child managed to walk without support by the age of 16 months. But later then he refused to walk and to bear weight on his lower limbs. Preceding history of gastroenteritis, swollen wrists and knee, bow legs, microcytic hypochromic anemia, mild hypocalcemia and marked hypophosphatemia is seen in severe form of the rickets. Raised alkaline phosphatase level is also seen.

Rickets occurs as a result of dietary deficiency of vitamin D. The diet of infants contains only small amount of vitamin D. Several factors predispose to vitamin D deficiency. Rickets particularly develops during rapid growth in low birth weight (LBW) and adolescents.

Bone consists of a protein matrix called osteoid and a mineral phase, principally composed of calcium and phosphate, mostly in the form of hydroxyapatite. Osteomalacia is present when there is inadequate mineralization of bone osteoid and occurs in children and adults.

Rickets is a disease of growing bone that is caused by unmineralized matrix at the growth plates and occurs in children only before fusion of the epiphyses. Because growth plate cartilage and osteoid continue to expand but mineralization is inadequate, the growth plate thickens. There is also an increase in the circumference of the growth plate and the metaphysis, increasing bone width at the location of the growth plates and causing some of the classic clinical manifestations, such as widening of the wrists and ankles.

There is a general softening of the bones that causes them to bend easily when subject to forces such as weight bearing or muscle pull. This softening leads to a variety of bone deformities. There is increase in overall bone turnover and concomitant rise in alkaline phosphatase.

Subsequent bone deformities result in cranio-tabes, greenstick fracture, impairment of the linear growth, rickety rosary, bowed legs, swollen wrist and knee. New bone formation is initiated by osteoblast. This is responsible for matrix deposits and its subsequent mineralization.

## ETIOLOGY

Vitamin D deficiency most commonly occurs in infancy because of a combination of poor intake and inadequate cutaneous synthesis. Trans-placental transport of vitamin D, mostly 25-D, typically provides enough vitamin D for the first 2 months of life unless there is severe maternal vitamin D deficiency. Infants who receive formula receive adequate vitamin D, even without cutaneous synthesis.

Because of the low vitamin D content of breast milk, breastfed infants rely on cutaneous synthesis or vitamin supplements. Cutaneous synthesis can be limited because of the ineffectiveness of the winter sun in stimulating vitamin D synthesis; avoidance of sunlight because of concerns about cancer, neighborhood safety, or cultural practices; and decreased cutaneous synthesis because of increased skin pigmentation.

## PATHOPHYSIOLOGY

Vitamin D deficiency causes decreased absorption of calcium from gut. The resulting hypocalcemia leads to increase in parathormone secretion. This helps in release of calcium from bone. Parathormone also reduces the excretion of calcium by kidneys and renal tubular absorption of phosphate. As a result, the serum calcium level tends to become normal, while the serum phosphate level falls.

After sometime, this compensatory mechanism fails and both calcium and phosphorous levels fall. Since calcium phosphate is necessary for deposition of calcium of growing bones, decrease in blood levels of calcium, phosphorous or both interfere with the calcification of the osteoid tissue. Serum alkaline phosphatase level also gets increased due to increase in osteoblastic activity.

Children with the disorder of the absorption such as celiac disease, steatorrhea, pancreatitis, cystic fibrosis may acquire rickets, because of deficient absorption of the vitamin D and calcium or both. This leads to lower serum calcium level. This in turn releases parathyroid hormone, restoring calcium to normal or near normal. This occurs at expense of the loss of phosphate in urine resulting in hypophosphatemia. The inorganic serum phosphate level is usually reduced to 0.5 mmol/L.

The other conditions which interfere with metabolic conversion and activation of vitamin D such as hepatic and renal lesions are also implicated in rickets.

## PATHOLOGY OF RICKETS

The epiphyseal plate is a narrow well-defined strip from where cartilage cells grow in parallel column towards the metaphysis. After initial proliferation, the old cartilage cells degenerate and disappear, leaving spaces into which the blood vessels and osteoblasts of the shaft can penetrate. Calcium is deposited in the zone of degenerating cartilage, which is then called “zone of preparatory calcification”.

In rickets, the cartilage cells go on multiplying giving rise to a broad irregular cartilaginous zone. The process of degeneration and calcification becomes incomplete, leading to softness of the bone. Rapidly growing cartilage cells particularly affect the costochondral junctions and end of long bones. There is also defective mineralization in the subperiosteal bone. In long-standing cases, the bones under stress may become deformed or even have pathological fractures.

Supplementation of vitamin D restores the normal development of the bone with calcification starting at the zone of preparatory calcification, which in a radiography would be seen as a thin dense line near the epiphysis.

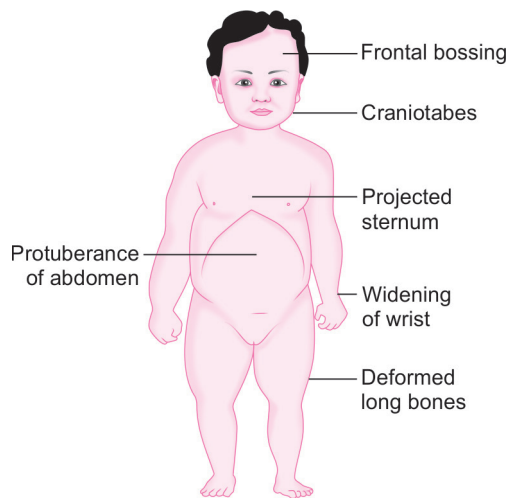
## CLINICAL FEATURES (FIG. 1)

Rickets is a disease of growing bones and its incidence is particularly high between 4 and 18 months. Skeletal deformities are the most striking feature of rickets.

Most manifestations of rickets are a result of skeletal changes. One of the early signs of rickets is craniotabes. Craniotabes is a softening of the cranial bones and can be detected by applying pressure at the occiput or over the parietal bones. The sensation is similar to the feel of pressing into a ping-pong ball and then releasing. It results from the thinning out of the inner table of the skull due to absorption of noncalcified osteoid tissue. Craniotabes may also be secondary to osteogenesis imperfecta, hydrocephalus, and syphilis. It is a normal finding in many newborns, especially near the suture lines, but it typically disappears within a few months of birth.

Other early evidences of osseous changes are, palpable enlargement of costochondral junctions, i.e., rachitic rosary and widening of the wrists and ankles (**Figs. 2 to 4**). Widening of the costochondral junctions results in a rachitic rosary, which feels like the heads of a rosary as the examiner's fingers move along the costochondral junctions from rib to rib. Growth plate widening is also responsible for the enlargement at the wrists and ankles.

The horizontal depression along the lower anterior chest known as Harrison groove occurs from pulling of the softened ribs by the diaphragm



**Fig. 1:** Clinical features.



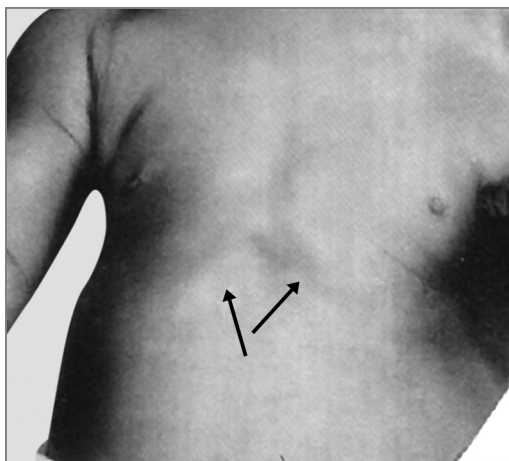
**Fig. 2:** Ricket rosary.



**Fig. 3:** Widened wrist.



**Fig. 4:** Widened ankle.



**Fig. 5:** Harrison sulcus.

during inspiration. Softening of the ribs also impairs air movement and predisposes patients to atelectasis and pneumonia.

Signs of advanced rickets can be easily recognized. Bossing of skull generally starts after the age of 6 months. It occurs due to heaping up of osteoid tissue in the frontal and parietal regions so that the skull appears squarish or box-like shape.

#### ESSENTIAL DIAGNOSTIC POINTS

- Bossing of skull
- Pigeon chest
- Harrison's groove
- Craniotabes
- Kyphosis
- Scoliosis
- Dwarfism
- Recurrent respiratory infection
- Hypotonia
- Distension of abdomen

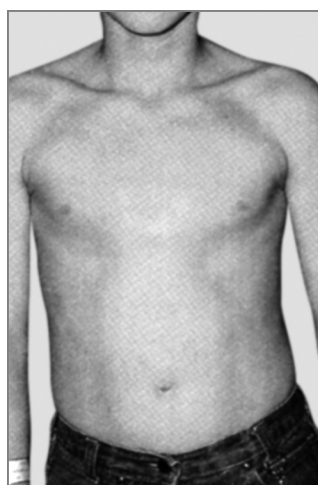
In thorax, the sternum is pushed forward, producing a "pigeon chest". A horizontal depression known as Harrison's groove, corresponding to costal insertion of the diaphragm develops (**Figs. 5 and 6**). The chest deformities (**Fig. 7**) decrease the lung resilience and predispose the child to intercurrent infections.

Bending of the spine backwards (kyphosis) and laterally (scoliosis) may occur. Pelvis may become softened and, the promontory of the sacrum is pushed anteriorly and the acetabulae inwards, resulting in a narrowed pelvic inlet. This is helped by lax ligaments. Deformity of a pelvis in a female, results in difficulty during labor at a later stage.

Long bones of the legs get deformed when the child starts bearing weight and is thus, usually seen after the age of 1 year. Bending of the femur,



**Fig. 6:** Pectus carinatum.



**Fig. 7:** Hyperexpand chest.



tibia and fibula, result in bow-legs or knock-knees (**Figs. 8 to 15**). Coxa vara and green stick fractures may also occur. All deformities of bones result in rachitic dwarfism.

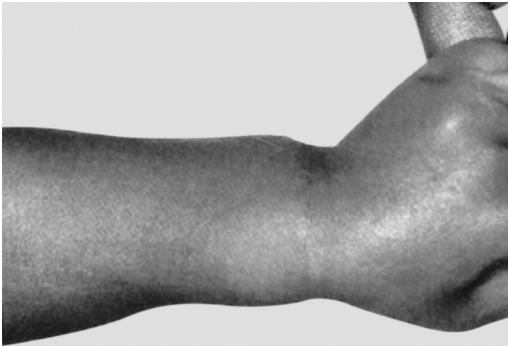
Dentition may be delayed and disordered eruption of temporary teeth occurs. In children between 8 and 18 months, permanent teeth, which are undergoing calcification, may be affected.



**Fig. 8:** Broad ankles—rickets.



**Fig. 9:** Genu valgum.



**Fig. 10:** Widening of the wrist.



**Fig. 11:** Broad wrists.



**Fig. 12:** Broad ankles.



**Fig. 13:** Bow legs.



Besides skeletal deformities, there is a generalized hypotonia with delay in motor development. The abdomen is protuberant, and generalized flabbiness of muscles may result into visceroptosis with downward displacement of spleen and liver.

Deficiency of vitamin D in early infancy results in bilateral lamellar cataracts. They may even be seen in neonatal period.

Clinical variants of rickets include type I—calcium deficient, type II—phosphate deficient and type III—end organ resistance to  $1,25(\text{OH})_2\text{D}_3$ .

#### GENERAL FEATURES

- Rachitic rosary
- Harrison's groove
- Delayed dentition
- Lumbar lordosis



Fig. 14: Knock knees.

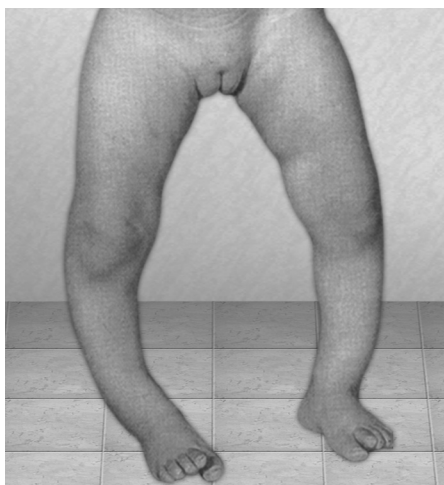


Fig. 15: Genu varum.

## DIAGNOSIS

The diagnosis of rickets is based on the clinical features, biochemical findings and characteristic radiological picture. The serum calcium level may be normal or low, the serum phosphorous level is below 4 mg/dL, and the serum alkaline phosphatase is usually elevated.

## Radiology

Radiological changes are best seen on postero-anterior radiographs of the wrist, although characteristic rachitic changes can be seen at other growth plates. Decreased calcification leads to thickening of the growth plate. The edge of the metaphysis loses its sharp border, which is described as *fraying*. The edge of the metaphysis changes from a convex or flat surface to a more concave surface. This change to a concave surface is termed *cupping* and is most easily seen at the distal ends of the radius, ulna, and fibula (**Fig. 16**). There is widening of the distal end of the metaphysis, corresponding to the clinical observation of thickened wrists and ankles as well as the rachitic rosary. Other radiologic features include coarse trabeculation of the diaphysis and generalized rarefaction.

Skiagram of the wrist shows widening, cupping and fraying of the epiphyses, in contrast to the normally sharply demarcated and slightly convex epiphyseal line. The density of shafts decreases with prominent trabeculae. There is an increase in distance between concave epiphyseal line and the ends of metacarpals. Green stick fractures, expansion of bone ends and bending of bones may be evident on radiographs. Some raising of

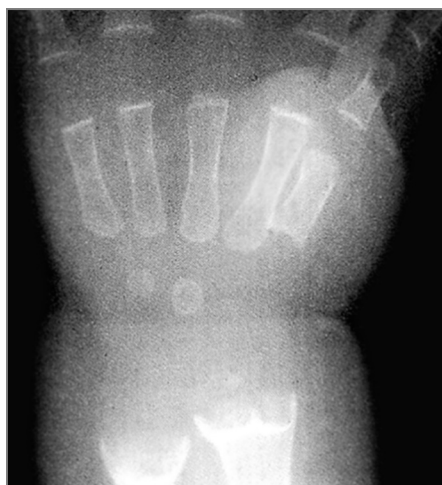


Fig. 16: Cup-shaped rarefied radius and ulna.

the periosteum is due to excess of osteoid lying under the periosteum.

The initial laboratory tests in a child with rickets should include serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), 25-hydroxyvitamin D, 1,25-dehydroxyvitamin D (1,25-D), creatinine, and electrolytes. The diagnosis of vitamin D deficiency is based on low circulating levels of 25OHD<sub>3</sub>. Values above 20 ng/mL are normal, between 10 and 20 ng/mL are insufficient and below 10 ng/mL are indicative of deficiency. Urinalysis is useful for detecting the glycosuria and aminoaciduria (positive dipstick for protein) seen with Fanconi syndrome. Evaluation of urinary excretion of calcium (24 hours collection for calcium or calcium creatinine ratio) is helpful if hereditary hypophosphatemic rickets with hypercalciuria or Fanconi syndrome is suspected. Direct measurement of other fat-soluble vitamins (A, E and K) or indirect assessment of deficiency (prothrombin time for vitamin K deficiency) is appropriate if malabsorption is a consideration.

If a good clinical examination does not provide a clue to etiology, then PTH should guide further workup. Primary and secondary hyperparathyroidism result in increased phosphorus leak from the proximal tubule. Thus, a child with any cause of calcipenic rickets, such as malabsorption or distal renal tubular acidosis, due to concomitant secondary hyperparathyroidism, may appear to have hypophosphatemic rickets. Serum PTH is a useful investigation at this juncture, being only marginally elevated in hypophosphatemic rickets, and significantly raised in calcipenic rickets.

Cases with high PTH should be investigated for distal renal tubular acidosis (RTA) by serum potassium, blood and urine pH, ammonium chloride loading test if necessary, and ultrasound of kidneys for nephrocalcinosis. Malabsorption tests include erythrocyte sedimentation rate, antidiomysial or tissue transglutaminase antibodies, D-xylose test and endoscopic duodenal biopsy. If these are negative, serum 25-OHD and 1,25(OH)<sub>2</sub>D can throw light on 1 alpha-hydroxylase defect and calcitriol receptor defect [Vitamin D-resistant rickets (VDRR) 1 and 21. Low PTH type of resistant rickets should be worked tip for phosphate clearance (phosphate Clearance/creatinine clearance) and TmP/GFR measurement. Proximal RTA is tested by bicarbonate loading test and documenting aminoaciduria, glycosuria and uric aciduria in addition to phosphaturia.

Plain radiology reveals coarse trabecular pattern in RTA and renal failure, and dense bone in hypophosphatemic rickets.

#### LABORATORY SALIENT FINDINGS

- Low serum phosphorus level
- High serum alkaline phosphatase level
- High PTH levels
- Low level serum calcifediol

#### Vitamin D Levels in Serum

	25-dihydroxyvitamin D level (ng/mL)
Deficient	<10
Insufficient	10–20
Optimal	20–60
High	60–90
Toxic	>90

Changes of active rickets in spine and pelvis are rarely seen even in advanced stages. The level of serum calcium is normal or slightly low (9–9.5 mg/dL), that of phosphate decreased (1.5–3 mg/dL). Serum alkaline phosphatase level is raised. PTH levels are normal. Blood levels of 1,25(OH)<sub>2</sub>D<sub>3</sub> are inappropriately low for the level of serum phosphate. Urinary phosphate excretion is increased with decreased tubular reabsorption of phosphate.

#### DIFFERENTIAL DIAGNOSIS

- Hypophosphatemia
- Metaphyseal dysostosis
- Fanconi's syndrome
- Cystinosis

Nutritional rickets should be differentiated from other types of rickets and chondrodystrophy. Other conditions producing bony deformities may, sometimes, need consideration. Craniotabes and a large head apart from rickets, occurs in hydrocephalus, congenital syphilis and osteogenesis imperfecta. Enlargement of costochondral junctions may also be seen in scurvy and chondrodystrophy.

#### TREATMENT

Children with nutritional vitamin D deficiency should receive vitamin D and adequate nutritional intake of calcium and phosphorus. There are two strategies for administration of vitamin D. With stoss therapy, 300,000–600,000 IU of vitamin D are administered orally or intramuscularly as two to four doses over 1 day. Because the doses are

observed, stoss therapy is ideal in situations where adherence to therapy is questionable.

The alternative is daily, high-dose vitamin D, with doses ranging from 2,000 to 5,000 IU/day over 4–6 weeks. Either strategy should be followed by daily vitamin D intake of 400 IU/day if <1 year old or 600 IU/day if >1 year old. It is important to ensure that children receive adequate dietary calcium and phosphorus; this dietary intake is usually provided by milk, formula, and other dairy products.

It is now advised to use lower daily doses of 2000 IU, 3000–6000 IU and 6000 IU for infants below 12 months, 1–12 years and more than 12 years for the duration of 12 weeks followed by maintenance dose of 400–600 IU/day.

Children who have symptomatic hypocalcemia might need intravenous calcium acutely, followed by oral calcium (30–75 mg/kg/day) supplements, which, typically can be tapered over 2–6 weeks in children who receive adequate dietary calcium. Transient use of intravenous or oral 1,25-D (calcitriol) is often helpful in reversing hypocalcemia in the acute phase by providing active vitamin D during the delay as supplemental vitamin D is converted to active vitamin D.

Calcitriol doses are typically 0.05 µg/kg/day. Intravenous calcium is initially given as an acute

bolus for symptomatic hypocalcemia (20 mg/kg of calcium chloride or 100 mg/kg of calcium gluconate). Some patients require continuous intravenous calcium drip, titrated to maintain the desired serum calcium level. These patients should transition to enteral calcium, and most infants require approximately 1,000 mg of elemental calcium.

Orthopedic corrective surgery, i.e., osteotomy is indicated for deformities. This is done only after active rickets is brought under control. Diet should be supplemented with adequate dose of vitamin D<sub>3</sub>. Steatorrhea or malabsorption of fat, should be treated. If there is no response even to the second dose, other variants of rickets should be looked for.

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## PRESENTING COMPLAINTS

An 18-month-old boy was brought with the complaints of:

- Decreased appetite since 2 months
- Irritability since 1 month
- Loose motion since 3–4 days
- Rashes since 2 days

## History of Presenting Complaints

An 18-month-old boy was brought to the hospital with history of irritability, digestive disturbance and loss of appetite. Her mother had noticed that her child was more irritable for last 2 months. She had even noticed that the child was becoming more irritable recently. Mother also complained that her son had on and off attack of loose motions, which were semisolid. She also complained that her son's appetite has come down drastically. She also made a note of development of small rashes over the recently. There was no history suggestive of hematuria.

### CASE AT A GLANCE

#### Basic Findings

Height	: 83 cm (90th centile)
Weight	: 10 kg (75th centile)
Temperature	: 37°C
Pulse rate	: 110 per minute
Respiratory rate	: 22 per minute
Blood pressure	: 60/40 mm Hg

#### Positive Findings

##### History

- Irritability
- Bowel disturbance
- Loss of appetite

##### Examination

- Frog-leg posture
- Hypertrophy of gums
- Subperiosteal hemorrhage
- Petechial hemorrhage
- Pallor
- Scorbutic rosary

##### Investigation

- *Hb*: Decreased
- *X-ray of the long bone*: Showed periosteal hematoma

## Past History of the Patient

He is the only child of nonconsanguineous marriage. He was born at full term by normal vaginal delivery. His birth weight was 2.5 kg. He started to take the breast milk immediately. Weaning started at 4th month. His developmental milestones were normal. He had been completely immunized. He was suffering from repeated respiratory tract infections.

## EXAMINATION

He was moderately built and nourished. Boy was irritable. There was evidence of generalized tenderness. He had assumed frog-leg posture. Hips and knees were semiflexed. Hypertrophy of the gums was present. There was prominent costochondral junction. Subperiosteal hemorrhages were palpated at the end of femur. Petechial hemorrhages were seen in skin and mucous membrane.

Anthropometric measurements included, the height was 83 cm (90th centile), the weight was 10 kg (75th centile), and the head circumference was 47 cm.

The child was afebrile. The heart rate was 110 per minute and the respiratory rate was 22 per minute. Blood pressure recorded was 60/40 mm Hg. Pallor was present. Cervical lymphadenopathy was present. There was no cyanosis and clubbing. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 9.3 g/dL
TLC	: 10,800 cells/cu mm
ESR	: 16 mm in the 1st hour
Platelet count	: 4,40,000 cells/cu mm
Bleeding time	: 6 minutes
Clotting time	: 10 minutes
X-ray of the long bone	: Showed features suggestive of periosteal hematoma

## DISCUSSION

In scurvy, there is defective formation of connective tissues and collagen in skin, cartilage, dentine, bone, and blood vessels, leading to their fragility. In the long bones, osteoid is not deposited by osteoblasts, cortex is thin, and the trabeculae become brittle and fracture easily.

Vitamin C is important for synthesis of collagen at the level of hydroxylation of lysine and proline in procollagen. It is also involved in neurotransmitter metabolism (conversion of dopamine to norepinephrine and tryptophan to serotonin), cholesterol metabolism (conversion of cholesterol to steroid hormones and bile acids), and the biosynthesis of carnitine. Vitamin C functions to maintain the iron and copper atoms, cofactors of the metalloenzymes, in a reduced (active) state. Vitamin C is an important antioxidant (electron donor) in the aqueous milieu of the body. Vitamin C enhances nonheme iron absorption, the transfer of iron from transferrin to ferritin, and the formation of tetrahydrofolic acid and thus can affect the cellular and immunologic functions of the hematopoietic system.

Vitamin C is potent reducing agent. The adrenals and lens have particularly high content of vitamin C. When a mother's intake of vitamin C during pregnancy and lactation is adequate, the newborn will have adequate tissue levels of vitamin C related to active placental transfer, subsequently maintained by the vitamin C in breast milk or commercial infant formulas. Breast milk contains sufficient vitamin C to prevent deficiency throughout infancy.

Absorption of vitamin C occurs in the upper small intestine by an active process or by simple diffusion when large amounts are ingested. Vitamin C is not stored in the body but is taken up by all tissues; the highest levels are found in the pituitary and adrenal glands.

Humans depend on dietary sources for vitamin C. An adequate intake is 40 mg for age 0–6 months and 50 mg for age 6–12 months. For older children, the recommended dietary allowance is 15 mg for age 1–3 years, 25 mg for age 4–8 years, 45 mg for age 9–13 years, and 65–75 mg for age 14–18 years. The requirement for vitamin C is increased during infectious and diarrheal diseases. The best food sources of vitamin C are citrus fruits and fruit juices, peppers, berries, melons, tomatoes, cauliflower, and green leafy vegetables.

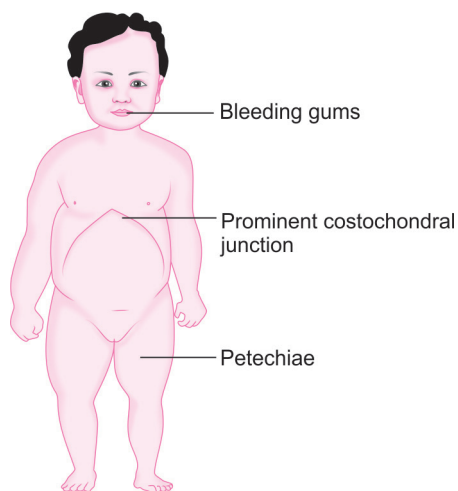
The need for vitamin C is increased by febrile illness, diarrheal disease, iron deficiency, and

exposure to cold. It is essential for the formation of collagen and intracellular matrix in teeth, bones and capillaries. It is also involved in tyrosine metabolism, adrenal cortical functioning and electron transport. It is a cofactor in activation of hydroxylating enzymes in oxidation process. It helps in the transfer of iron from the plasma transferrin into tissue ferritin and thus helps in storage of iron in the bone marrow, spleen, and liver. It provides protection to eyes and lungs against oxidizing agents. Hence, it reduces oxidation of low density lipoprotein and prevents the deposition of atheromatous plaque. It helps in maintenance of vascular integrity through the prostacyclin, i.e., antiplatelet and vasodilating effect.

Ascorbic acid is essential for normal formation of collagen. Alteration in collagen formation is partly due to failure to incorporate hydroxyproline and proline. Formation of collagen and chondroitin sulfate is impaired. The periosteum becomes loosened. Subperiosteal hemorrhages occur especially at ends of femur and tibia. In severe scurvy, there may be degeneration in the skeletal muscles, cardiac hypertrophy, bone marrow depression, and adrenal atrophy.

## CLINICAL FEATURES (FIG. 1)

Scurvy may occur at any age. The usual age of onset is 6–18 months. Breastfed infants are well protected in breast milk contains adequate amount of vitamin C. Clinical manifestations require time to develop. The symptoms may include irritability, tachypnea, digestive disturbances, and loss of appetite.



**Fig. 1:** Clinical features.



Irritability becomes progressive. There is evidence of generalized tenderness. Pain results in pseudoparalysis. Child will assume frog-leg position. Hips and knees are semiflexed with feet rotated outward. Subperiosteal swelling can be palpated at the end of femur. Hypertrophy of gums (**Figs. 2 and 3**) is present. There may be scorbutic rosary at the costochondral junction.

Subperiosteal hemorrhages in the lower limb bones sometimes acutely increase the swelling and pain, and the condition might mimic acute osteomyelitis or arthritis. Costochondral junction becomes prominent and appears sharp and angular, scorbutic rosary is attributed to the separation of epiphyses of ribs and backward displacement of sternum. A “rosary” at the costochondral junctions and depression of the sternum are other typical features. The angulation of scorbutic beads is usually sharper than the angulation of a rachitic rosary. Gum changes are seen in older children after teeth have erupted and are manifested as bluish purple, spongy swellings of the mucous membrane, especially over the upper incisors. Gum bleeds are common (**Fig. 4**).

Anemia, a common finding in infants and young children with scurvy, is related to impaired iron absorption and coexistent hematopoietic nutrient deficiencies including iron, vitamin B<sub>12</sub>, and folate. Hemorrhagic manifestations of scurvy include petechiae, purpura, and ecchymoses at pressure points; epistaxis; gum bleeding; and the characteristic perifollicular hemorrhages. Other manifestations are poor wound and fracture healing, hyperkeratosis of hair follicles, arthralgia, and muscle weakness.

Petechial hemorrhages occur in skin and mucous membrane. Hematuria, melena or orbital, conjunctival and subdural hemorrhage may be found. The anemia is associated with that of scurvy. These are sickle cell anemia, iron deficiency anemia, and sometimes dimorphic anemia.

#### ESSENTIAL DIAGNOSTIC POINTS

- Irritability, generalized tenderness
- Pseudoparalysis, frog-leg position
- Bleeding and hypertrophy of gums
- Prominent costochondral junction
- Petechial hemorrhage in skin mucous membrane
- Orbital and conjunctival hemorrhage

#### GENERAL FEATURES

- Child is listless
- Anorexia
- Paradoxical cry
- Frog-like posture
- Hemorrhages



**Fig. 2:** Gingival hypertrophy.  
(For color version see Plate 7)



**Fig. 3:** Gum hypertrophy.  
(For color version see Plate 7)



**Fig. 4:** Bleeding gum.  
(For color version see Plate 7)

## DIAGNOSIS

The typical radiographic changes occur at the distal ends of the long bones and are particularly common at the knees. The shafts of the long

bones have a ground-glass appearance because of trabecular atrophy. The cortex is thin and dense, giving the appearance of pencil outlining of the diaphysis and epiphysis. Epiphyseal ends are sharply outlined.

The white line of Frankel, an irregular but thickened white line at the metaphysis, represents the zone of well-calcified cartilage. White line may also be seen with healing rickets, severe protein-energy malnutrition (PEM), plumbism, acute leukemia, and congenital syphilis. Epiphyseal centers of ossification are surrounded by white ring—Wimberger's sign.

The epiphyseal centers of ossification also have a ground-glass appearance and are surrounded by a sclerotic ring. The more specific but late radiologic feature of scurvy is a zone of rarefaction under the white line at the metaphysis. This zone of rarefaction (Trümmerfeld zone), a linear break in the bone that is proximal and parallel to the white line, represents area of debris of broken-down bone trabeculae and connective tissue.

A Pelkan spur is a lateral prolongation of the white line and may be present at cortical ends. Epiphyseal separation can occur along the line of destruction, with either linear displacement or compression of the epiphysis against the shaft. Subperiosteal hemorrhage produces periosteal elevation.

Evidence of vitamin C deficiency is better furnished by ascorbic acid concentration in

white cells, platelet layer (buffy layer) of centrifuged oxalated blood. A level of zero in this layer indicates latent scurvy.

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes arthritis, acrodynia, osteomyelitis, pseudoparalysis, syphilis, poliomyelitis, and leukemia.

## TREATMENT

Administration of ascorbic acid is preferred. The only therapeutic dose is 100–200 mg or more orally or parenterally. Three to four ounces of orange or tomato juice will be of help.

Vitamin C supplements of 100–200 mg/day orally or parenterally ensure rapid and complete cure. The clinical improvement is seen within a week in most cases, but the treatment should be continued for up to 3 months for complete recovery.

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# Ewing's Sarcoma

## PRESENTING COMPLAINTS

A 3-year-old boy was brought with the complaints of:

- Swelling in the right leg since 2 months
- Pain in the leg since 15 days
- Fever since 7 days
- Not able to walk since 2 days

## History of Presenting Complaints

A 3-year-old boy was brought to the hospital with the history of pain in the right leg. Mother told that he had been complaining of pain in right leg for the last 2 weeks. Mother also told that child had fever since last 1 week. Fever was moderate to high degree, intermittent. It was not associated with chills and rigors. It used to be more in the evening. Child was not able to walk because of pain in the leg. He was limping. Mother had also noted that there was a small swelling in the leg.

### CASE AT A GLANCE

#### Basic Findings

Height	: 93 cm (50th centile)
Weight	: 13 kg (75th centile)
Temperature	: 38°C
Pulse rate	: 120 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Pain
- Fever
- Swelling

##### Examination

- Tenderness
- Limping
- Swelling
- Febrile

##### Investigation

- *X-ray of leg*: Irregularly thickened cortical wall
- *FNAC*: Small uniform round cells

## Past History of the Patient

He was the only sibling of consanguineous marriage. He was born at full term by normal vaginal delivery. He cried immediately after the delivery. He started taking feeds as early as possible. There was no significant postnatal event. He was sent home on 3rd day. Weaning started from 4th month as per advice by family doctor. He was on family food by 1 year. All the developmental milestones were normal. He had been completely immunized.

## EXAMINATION

The child was moderately built and nourished. He was not allowing anybody to touch his right leg. Anthropometric measurements included, his height was 93 cm (50th centile), and the weight was 13 kg (75th centile).

He was febrile, the heart rate was 120 per minute, and the respiratory rate was 20 per minute. The blood pressure recorded was 70/50 mm Hg. There was no pallor. Right inguinal lymph nodes were enlarged and tender. There was erythema and tenderness at the upper part of right leg.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 7,800 cells/cu mm
ESR	: 32 mm in the 1st hour
AEC	: 330 cells/cu mm
X-ray chest	: NAD
X-ray of the leg	: Irregularly thickened cortical wall of the proximal half of the tibia
Bone marrow biopsy	: NAD
CT scan chest	: NAD
FNAC	: Small uniform round cells

## DISCUSSION

It is a small round blue cell tumor of the bone. It is more common in male. The primary symptom

is pain. This may be accompanied by fever and tenderness. The soft tissue involvement varies but may be massive.

Other conditions that may be confused are osteomyelitis and eosinophilic granuloma. Ewing's sarcoma and primitive neuroectodermal tumor is the second most common malignant bone tumor, after osteogenic sarcoma in children and adolescents.

Ewing sarcomas may arise in the bone or soft tissues throughout the body. They may be undifferentiated (pathologically termed Ewing sarcoma) or show evidence of neural differentiation (pathologically termed primitive neuroectodermal tumor or PNET). Moreover, a subset of these tumors that arise in the chest wall have historically been referred to as Askin tumors. As Ewing sarcoma, PNET, and Askin tumors are now understood to share the same fundamental biology, the principles that drive the management of patients with these tumors are largely identical.

It is an uncommon type of highly malignant small round cell undifferentiated bone tumor occurring in children. Ewing's tumor forms about 20% of all malignant bone tumors. It occurs in the age group of 10–20 years and is more common in males. It can also be seen below the age of 10 years. It arises from the primitive mesenchymal cells of the medullary cavity. The sites affected are the diaphyseal regions of long bones like femur, tibia and humerus. It also occurs in flat bones like pelvic bones.

## **PATHOGENESIS**

Additionally, MIC-2 (CD99) staining is usually positive. A specific chromosomal translocation, t (11;22), or a variant thereof is found in most of the Ewing sarcoma family of tumors. The feature of Ewing sarcoma is the presence of one of several recurrent chromosomal translocations involving members of the ten-eleven translocation (TET) transcription factor family and erythroblast transformation-specific (ETS) transcription factor gene family members. The translocation results in a novel chimeric transcription factor that brings the activation domain of the TET family with the deoxyribonucleic acid (DNA) binding domain of the ETS family member. Analysis for the chain reaction translocation by fluorescent in situ hybridization (FISH) or polymerase analysis for the chimeric fusion gene products EWS/FLI-1 or EWS/ERG is utilized routinely in diagnosis. The most common translocation involves EWSR1 (Ewing sarcoma 1) on chromosome 22 with FLI-1

on chromosome 11, leading to the classic t (11; 22) translocation. These fusions are believed to be the initiating event in the development of these tumors.

Immunohistochemical staining assists in the diagnosis of Ewing sarcoma to differentiate it from small, round, blue cell tumors such as lymphoma, rhabdomyosarcoma, and neuroblastoma. Histochemical stains may react positively with certain neural markers on tumor cells (neuron-specific enolase and S-100), especially in peripheral primitive neuroectodermal tumors. Reactivity with muscle markers (e.g., desmin, actin) is absent.

## **PATHOLOGY**

These tumors can arise in any bone. But the most common sites are flat bones such as pelvis, chest wall, head, vertebrae and the diaphyseal region of long bones. The most commonly involved bone is femur. The most common sites of metastasis are lungs, bone marrow, central nervous system and other bones.

Macroscopically the tumor is a pale soft mass with minimal bone tissue. There are areas of degeneration and hemorrhage. There is further simulation of osteomyelitis by the presence of milky pus-like fluid in the tumor tissue due to degeneration.

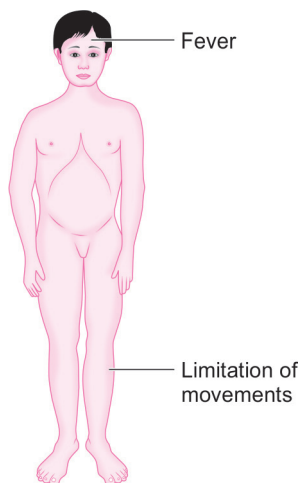
Microscopically the tumor is very cellular with minimal stromal tissue. The characteristic cell is the small polyhedral cell with scanty cytoplasm and large nucleus. The appearance is monotonously uniform with cells arranged in compact sheets with loose and vacuolated formation by the tumor cells. This stimulates the rosette formation of neuroblastoma. Presence of glycogen helps in differentiating this condition from neuroblastoma. This is indicated by periodic acid-Schiff (PAS) reaction. The tumor must be differentiated from lymphoma (reticulum cell sarcoma).

### **ESSENTIAL DIAGNOSTIC POINTS**

- Small, round blue cell malignancy
- Pain, swelling
- Fever, anemia, leukocytosis
- Weight loss

## **CLINICAL FEATURES (FIG. 1)**

The patient presents with pain which gradually increases and is followed by a swelling. The swelling is firm to soft in consistency with indefinite margins. The duration of the symptoms may vary from few weeks to few months and sometimes more than 1 year. The most common presenting symptom is pain, and occasionally swelling will



**Fig. 1:** Clinical features.

occur, depending on the location and size of the primary tumor. As patients with Ewing sarcoma tend to be otherwise healthy, active adolescents, it is not unusual for initial musculoskeletal complaints to be attributed to injury, often responsive to nonsteroidal anti-inflammatory drugs, and for there to be repeated visits for persistent pain prior to diagnosis. Some patients have a palpable mass at initial presentation, and some may have functional consequences related to the location of the tumor.

Ewing sarcoma often is associated with systemic manifestations, such as fever and weight loss; patients may have undergone treatment for a presumptive diagnosis of osteomyelitis fever of unknown origin. Patients also may have a delay in diagnosis when their pain or swelling is attributed to a sports injury.

The swelling rapidly increases in size with involvement of soft tissues and the general condition deteriorates. The peculiar feature of Ewing's tumor is that metastasis occur in other bones like skull, vertebrae and ribs, in addition to the lungs by spread through bloodstream.

Approximately 80% of patients have a primary tumor arising from a bone, while the other 20% have, soft tissue primary tumors. Among patients with bone tumors, approximately half of cases will arise in the long bones of the extremities while the other half will arise in flat bones such as the pelvis and ribs, a distribution that is markedly different from pediatric osteosarcoma, which is predominantly a disease of the long bones. Metastatic disease is present at initial diagnosis in a quarter of cases, with lung, bone, and bone marrow being the most common metastatic sites.

### GENERAL FEATURES

- Pain
- Swelling
- Weight loss

### DIAGNOSIS

Once a diagnosis of Ewing sarcoma is established, staging studies are performed to assess for the presence of disseminated disease. Patients require CT of the chest and staging for bone metastases, either with a bone scan or whole-body positron emission tomography (PET) scan. Positron emission tomography scanning has become more prevalent in recent years and appears to be more sensitive than bone scans in detecting metastatic disease. For bone marrow staging, bilateral bone marrow aspirates and biopsies are commonly performed, though recent evidence indicates that PET imaging results may guide the need for whether or not bone marrow biopsies should be performed. Some centers do not perform staging bone marrow biopsies in patients who have no evidence of metastatic disease by PET scans, as there is a low likelihood of isolated metastatic disease to the bone marrow.

Ewing's sarcoma occurs primarily between 10 and 20 years. It is suspected from clinical history and radiographic features. It should be confirmed by surgical biopsy. Once the diagnosis is made the patients should be screened for metastasis in lung.

Radiograph shows areas of mottled rarefaction in the affected diaphysis of bone. There will be marked destruction of the bone cortex and involvement of the soft tissues. There is also reactive new bone formation in layers under the raised periosteum producing the characteristic "onion-peel" appearance. A large, associated, soft tissue mass often is visualized on MRI or CT, the differential diagnosis includes osteosarcoma, osteomyelitis, Langerhans cell histiocytosis, primary lymphoma of bone, metastatic neuroblastoma, or rhabdomyosarcoma in the case of a pure soft tissue lesion.

CT-guided surgical biopsy of the lesion often provides diagnostic tissue. It is important to obtain adequate tissue for special stains and molecular studies. Computed tomography scan of bone and marrow biopsy are advised. Pathological fracture may occur through the bone as a result of tumor destruction or at a biopsy site. They may heal poorly during radiotherapy and chemotherapy. This may cause pain.

Special histochemical staining should be done to distinguish Ewing's sarcoma from other metastatic



round cell tumor like rhabdomyosarcoma, neuroblastoma or non-Hodgkin lymphoma.

Thorough evaluation for metastatic disease includes CT of the chest, radionuclide bone scan, and bone marrow aspiration and biopsy specimens from at least two sites. MRI of the tumor and the entire length of involved bone should be performed to determine the exact extension of the soft tissue and bony mass and the proximity of tumor to neurovascular structures.

Ewing sarcoma is a classic small round blue cell tumor, characterized pathologically by sheets of monomorphic cells with a high nuclear-to-cytoplasmic ratio. Immunohistochemistry and cytogenetic/molecular studies are critical to differentiate Ewing sarcoma from other childhood small round blue cell tumors. Cluster of differentiation 99 (CD99), while not specific to Ewing sarcoma, is the most useful stain, with a strong membranous pattern classically described. Additional testing to confirm a diagnosis will include cytogenetic studies such as FISH that reveal a break at the EWSR1 locus, or polymerase chain reaction (PCR) to assess and detect a specific EWS-ETS translocation.

#### LABORATORY SALIENT FINDINGS

- CT scan, MRI of the primary lesion
- CT scan of the chest
- Bone scanning, bilateral bone marrow aspirates and biopsy
- Special histochemical staining
- *Radiograph*: Onion-peel appearance

### DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes osteosarcoma, osteomyelitis, eosinophilic granuloma, lymphoma, rhabdomyosarcoma and neuroblastoma.

### TREATMENT

Ewing sarcoma is considered a radiosensitive tumor, and local control may be achieved with irradiation or surgery. Radiation therapy is associated with a risk of radiation induced second malignancies, failures of bone growth, fibrosis. It is the traditional treatment of Ewing's tumor. This tumor is radio-sensitive and regression following therapy is remarkable.

However with this type of treatment, the local recurrence rate is high. Hence, currently after preoperative chemotherapy, surgical resection of the tumor bearing bone is done with skeletal

reconstruction followed by postoperative chemotherapy. This regimen has increased the survival rate from 5 to 50%. Surgical resection is indicated to achieve local control. Chemotherapy should be resumed as soon as possible after surgery. Tumor control with radiotherapy requires moderately high doses ranging from 5.500 cGy to 6.000 cGy.

Multiagent chemotherapy is important because it can shrink the tumor rapidly and is usually given before local control is attempted. Standard chemotherapy for nonmetastatic Ewing sarcoma includes vincristine, doxorubicin, cyclophosphamide, etoposide, and ifosfamide. Chemotherapy usually causes dramatic shrinkage of the soft tissue mass and rapid, significant pain relief.

Ewing sarcoma is considered a radiosensitive tumor, and local control may be achieved with irradiation or surgery. Radiation therapy is associated with a risk of radiation-induced second malignancies.

### PROGNOSIS

Stage at initial diagnosis is the strongest clinical prognostic factor for Ewing sarcoma. Approximately 70% of patients with localized disease can be expected to survive at least 5 years without relapse or progression with contemporary therapy, compared to only 30% or less for patients with metastatic disease. Among patients with metastatic disease, location of metastases appears to have important prognostic value, as those with bone and/or bone marrow metastasis have dismal outcomes compared to those with isolated pulmonary metastatic disease. Other adverse prognostic factors at initial presentation include older age, larger tumor size, and primary pelvic site. Poor response to initial chemotherapy, based upon imaging and/or histopathology, is also associated with inferior outcomes.

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# Hodgkin's Disease

## PRESENTING COMPLAINTS

A 7-year-old girl was brought with the complaints of:

- Swelling in the neck since 6 months
- Fever since 15 days
- Tiredness since 1 week

## History of Presenting Complaints

A 7-year-old girl came to the pediatric outpatient department, referred by a general practitioner for evaluation of swelling of neck. The girl's mother had noticed a small swelling on the left side of the neck of her daughter about 6 months back. Then she was taken to their family doctor. Doctor told her that it could be because of the respiratory tract infection and a course of antibiotics was given. But the increasing swelling still persisted. It was gradually increasing in size, but the girl

did not complain of pain or tenderness at any time. Then again mother took the child to her family doctor. This time he referred for evaluation to the hospital.

Mother also told that there was history of fever which was mild-to-moderate degree. This was not associated with chills and rigors. Fever used to be more in the evening. Mother also gave the history of loss of appetite and loss of weight. The girl also complained early fatigability.

## Past History of the Patient

She was the first child of consanguineous marriage. She was born at term with normal vaginal delivery. She cried immediately after delivery. She started taking feeds, i.e., breastfeeds immediately, weaning started by the age of 4 months and completed by 1 year. Her developmental milestones were normal. Her performance at school was above average.

## CASE AT A GLANCE

### Basic Findings

Height	: 118 cm (50th centile)
Weight	: 18 kg (25th centile)
Temperature	: 37°C
Pulse rate	: 100 per minute
Respiratory rate	: 22 per minute
Blood pressure	: 70/60 mm Hg

### Positive Findings

#### History

- Swelling in the neck
- Anorexia
- Fever
- Weight loss

#### Examination

- Poorly built
- Nontender swelling
- Pallor
- Splenomegaly

#### Investigation

- Hb: Anemia
- Excision biopsy: Presence of Reed-Sternberg cells
- ESR: Raised

## EXAMINATION

The girl was moderately built and poorly nourished. She was sitting comfortably on the examination table. There was an anxious look in her eyes. Her anthropometric measurements included, the height was 118 cm (50th centile) and the weight was 18 kg (25th centile).

She was afebrile, the heart rate was 100 per minute, and the respiratory rate was 22 per minute. The blood pressure recorded was 70/60 mm Hg.

She was pale and the swelling was present on the left part of the neck measuring about 3 × 4 cm. The swelling was nontender, rubbery in consistency there was matting. There was no change in the skin. The lymph nodes were discrete and mobile. There was no icterus and no cyanosis.

Per abdomen examination revealed presence of splenomegaly measuring about 3 cm below the costal margin. There was no hepatomegaly. Cardiovascular and respiratory system were normal.

## INVESTIGATION

Hemoglobin	: 9 g/dL
TLC	: 8,600 cells/cu mm
DLC	: P <sub>62</sub> L <sub>30</sub> E <sub>8</sub>
ESR	: 56 mm in the 1st hour
AEC	: 506 cells/cu mm
Mantoux test	: Negative
Chest X-ray	: NAD
Excision biopsy	: Presence of Reed–Sternberg cells

## DISCUSSION

A child with history of painless swelling at the neck, loss of appetite, loss of weight and presence of splenomegaly along with excision biopsy findings suggests lymphoma.

Hodgkin's disease (HD) is a malignant disorder of lymphoreticular system. The Reed–Sternberg (RS) cell represents the malignant cell in HD. It is characterized by progressive enlargement of lymph nodes. The disease is usually considered unicentric in origin. It has a predictable pattern of spread by extension to contiguous nodes. This is one of the lymphoreticular malignancies. It is associated with impaired cellular immunity in host.

The incidence is highest in late childhood and early adulthood (15–35 years). It is very uncommon under 5 years of age and almost never seen under 2 years of age. The sex ratio progresses from one of male preponderance of 10:1 under the age of 7 years falling to 1.1:1 after the age of 12 years.

Infectious agents may be involved, such as human herpesvirus 6, cytomegalovirus, and Epstein–Barr virus (EBV). The role of EBV is supported by prospective serologic studies. Infection with EBV confers a 4-fold higher risk of developing Hodgkin's lymphoma (HL) and may precede the diagnosis by years. EBV antigens have been demonstrated in HL tissues, particularly type II latent membrane proteins 1 and 2, although EBV status is not thought to be prognostic of outcome.

A genetic predisposition to HL is suggested by the variation in incidence, among racial and ethnic groups, familial aggregation of the disease, and association with specific human leukocyte antigens. Many investigators have observed concordance of HL in first-degree relatives, including sibling and parent–child pairs. Standardized incidence ratios range from 3-fold for parent–child pairs to over 50-fold for monozygotic twins. HL also develops more frequently in individuals with congenital or acquired immunodeficiency, leading to the

speculation that an inherited subtle immune abnormality may predispose to the development of HL by increasing the risk of malignant transformation induced by environmental factors. Genome-wide association studies have identified HLA and non-HLA susceptibility loci.

Classical HL has a bimodal incidence, with a first peak among adolescents and young adults and another among adults in the seventh to eighth decade of life. The young adult form (ages 15–34 years) shows a predominance of the nodular sclerosing histologic subtype in white adolescents and young adults in developed countries. HL is uncommon among preadolescent children, where it is associated with poorer socioeconomic environments, male sex, EBV infection, and the mixed cellularity histologic subtype.

Hodgkin's lymphoma is more common in males than in females in all parts of the world. The male predominance is most marked in patients younger than age 10 years. In adolescents, the gender difference in incidence is less conspicuous, particularly for the nodular sclerosing histologic subtype.

## PATHOLOGY

Normal architecture of the lymph nodes is distorted. Architecture is pleomorphic with varying number of lymphocytes. Giant cells with the mirror image called RS cells are found. RS can be seen in reactive lymphoid hyperplasia, non-Hodgkin's lymphoma and in non-lymphoid malignancies. Histologically, the lesions are classified as:

- Lymphocyte—predominant (10–20%)
- Nodular sclerosis (most common type) (40–60%)
- Mixed cellularity (20–40%)
- Lymphocyte—depleted (5–10%)

## PATHOGENESIS

The RS cell, a pathognomonic feature of HL, is a large cell (15–45 µm in diameter) with multiple or multilobulated nuclei. This cell type is considered the hallmark of HL, although similar cells are seen in infectious mononucleosis, non-Hodgkin lymphoma (NHL), and other conditions. The RS cell is clonal in origin and arises from the germinal center B cells but typically has lost most B-cell gene expression and function, i.e., malignant transformation. EBV has been linked to HD and suggests EBV activation may contribute to the HD.

This typically leads to cell regulation defects such as constitutive activation of the nuclear factor-κB pathway or abnormal regulation of the

Bcl-2 family of proteins. HL, is characterized by a variable number of RS cells surrounded by an inflammatory infiltrate of lymphocytes, plasma cells, and eosinophils in different proportions, depending on the HL histologic subtype. The interaction between the RS cell and these background inflammatory cells with their associated cytokine release is important in the development and progression of HL.

Reactive infiltration of eosinophils and CD68+ macrophages, and increased concentrations of cytokines, such as interleukins 1 and 6 and tumor necrosis factor, are all associated with an unfavorable prognosis, including advanced stage, the presence of "B" symptoms (constitutional): decreased response to therapy, and reduced survival.

### CLINICAL FEATURES (FIG. 1)

Hodgkin's disease has an insidious onset. The most common presentation is (80%) of patients is painless cervical lymphadenopathy, of whom 60% have symptomatic involvement of the mediastinum.

Patients commonly present with painless, nontender, firm, rubbery, cervical or supraclavicular lymphadenopathy and usually some degree of mediastinal involvement. They may be discrete or matted together and are fixed surrounding tissue.

There is painless enlargement of lymph node which occurs usually on one side. This progressively involves adjacent nodes. Posterior cervical lymph nodes are easily affected. Initially auxiliary and anterior mediastinal lymph nodes are involved. The deeper lymph nodes may cause

pressure on surrounding structures and produce related symptoms.

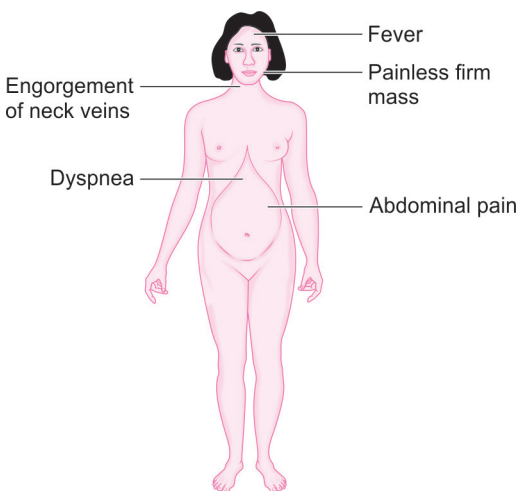
Mediastinal compression may cause dysphagia, dyspnea or brassy cough. Engorgement of the neck veins and hoarseness are due to pressure on the neck veins and recurrent laryngeal nerve. Depending on the extent and location of nodal and extranodal disease, patients may present with symptoms and signs of airway obstruction (dyspnea, hypoxia, cough), pleural or pericardial effusion, hepatocellular dysfunction, or bone marrow infiltration (anemia, neutropenia, or thrombocytopenia). Uncommon extranodal sites are central nervous system (CNS), bone, gastrointestinal tract (GIT) and skin. A reduced cell mediated immunity results in an increase susceptibility to infections.

Lymph node biopsy (**Table 1**) is indicated lack of identifiable infection in the region drained by enlarged node, a node greater than 2 cm in size, supraclavicular adenopathy or abnormal chest X-ray lymphadenopathy increasing in size after 2 weeks or failing to resolve within 4–8 weeks.

Retroperitoneal lymph nodes may cause abdominal pain, lymph nodes are discrete, mobile and nontender. Fever, anemia, anorexia, and weight loss develop within few months after enlargement of lymph nodes.

Hematogenous spread involves liver, spleen, bone and bone marrow (**Table 2**). This will lead to systemic symptoms. Constitutional or class "B" symptoms are more common with advanced disease (stage I—5%, stage IV—81%) and are associated with a poorer outcome. Systemic symptoms, (constitutional) classified as B symptoms that are considered important in staging, are unexplained fever (100.4°F), weight loss >10% total body weight over 6 months, and drenching night sweats. The type of the fever noted in HD is Pel-Ebstein type. There will be regular alteration of recurrent bouts of fever and afebrile state.

Active autoimmune conditions Pel-Ebstein type are occasionally coexistent at the time of diagnosis with HL. The most common among these are autoimmune cytopenias: Coombs'-positive hemolytic anemia and immune thrombocytopenic purpura (ITP). Both tend to resolve with the initiation of HL-directed therapy. Other abnormalities of the immune system can either predate or present concurrently with a diagnosis of HL, including enhanced sensitivity to suppressor T-lymphocytes and reduction of natural killer cell cytotoxicity, leading to deficient cell-mediated immunity.



**Fig. 1:** Clinical features.

**TABLE 1:** Histopathological classification of Hodgkin's disease.

<i>Rye</i>	<i>Distinctive features</i>
Lymphocyte predominant (LP)	Benign appearing lymphocytes with or without histiocytes. Few Reed–Sternberg (RS) cells. No fibrosis
Nodular sclerosis (NS)	Thickened capsule with proliferation of orderly collagenous bands, that divide lymphoid tissue in nodules: Lacunar variant of RS cells
Mixed cellularity (MC)	5–15 RS cells per high power field. Fine fibrosis in interstitium. Focal necrosis may be present
Lymphocyte depletion (LD)	Abnormal cells with relative paucity of lymphocytes. Fibrosis and necrosis common but diffuse

**TABLE 2:** Modified Ann Arbor classification of Hodgkin's disease.

<i>Stage</i>	<i>Description</i>
I	Involvement of single lymph node region (I) or of a single extra lymphatic organ or site (I <sub>e</sub> ) by direct extension
II	Involvement of two or more lymph node regions on the same side of diaphragm (II) or localized involvement of an extra-lymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm Abdominal disease is limited to the upper abdomen (i.e., spleen, splenic hilar nodes, celiac nodes, porta hepatic nodes)
III <sub>2</sub>	Involvement of lymph node regions on both sides of the diaphragm Abdominal disease includes para-aortic, mesenteric and iliac involvement with or without disease in the upper abdomen
IV	Disseminated involvement of one or more extra-lymphatic organs or tissues with or without associated lymph node disease
A	No symptoms
B	Fever, night sweats or weight loss of more than 10% of body weight in the previous 6 months
X	Bulky disease (greater than 10 cm in maximum dimension; greater than one-third of the internal transverse diameter of the thorax at the level T5/T6)
E	Limited involvement of a single extranodal site
CS	<i>Clinical stage:</i> When based solely on physical examination and imaging technique
PS	<i>Pathologic stage:</i> When based on biopsies

## Clinical Staging of Hodgkin's Disease

Currently, the clinical staging can be done by computed tomography (CT) scan or gallium scan.

*Stage I* : Lymph nodes in a single anatomic zone are affected.

*Stage II* : Lymph nodes of two or more contiguous or adjacent regions are involved. All of them are on the same side of the diaphragm.

*Stage III* : Lymphatic tissues are enlarged on both sides of diaphragm but are limited to lymph nodes, Waldeyer's ring and spleen.

*Stage IV* : Involvement of the visceral organs.

Stages II and III are subdivided. Those without constitutional symptoms are denoted by (a), and those associated with constitutional symptoms by (b).

### ESSENTIAL DIAGNOSTIC POINTS

- Painless cervical or supraclavicular adenopathy
- Mediastinal mass in 50%
- Fatigue, anorexia, weight loss
- Fever, night sweats, pruritis, cough

### GENERAL FEATURES

- Anemia
- Anorexia
- Dysphagia
- Brassy cough
- Nephrotic syndrome

## DIAGNOSIS

Evaluation includes history, physical examination, and imaging studies including chest radiograph; CT scans of the neck, chest, abdomen, and pelvis; and positron emission tomography (PET) scan.

Laboratory abnormalities in HL are non-specific, usually indicating an inflammatory state, with activation of the reticuloendothelial system and subsequent acute phase reactants. Frequent findings include elevation of the erythrocyte sedimentation rate, ferritin, and C-reactive protein, as well as a normocytic anemia of chronic inflammation. Elevations of serum lactate dehydrogenase or alkaline phosphatase are less common.

A chest radiograph is particularly important for measuring the size of the mediastinal mass in relation to the maximal diameter of the thorax. Chest CT more clearly defines the extent of a mediastinal mass if present and identifies hilar nodes and pulmonary parenchymal involvement, which may not be evident on chest radiographs.

CT scan of the chest provides information about pulmonary parenchyma, chest wall, pleura



and pericardium that may not be apparent on chest X-ray. CT scan of the abdomen and pelvis is done to examine for involvement of the viscera and lymph nodes. Although lymphangiography is a reliable method for retroperitoneal lymph nodes, it is rarely performed in children. Bone marrow biopsy should be performed in all children with systemic symptoms and in advanced stage (III and IV) disease. A staging laparotomy is not performed because of concerns related to operative morbidity and splenectomy.

Formal excisional biopsy is preferred over needle biopsy to ensure that adequate tissue is obtained, both for light microscopy and for appropriate immunohistochemical and molecular studies. Once the diagnosis of HL, is established, extent of disease (stage) should be determined to allow selection of appropriate therapy.

Bone marrow aspiration and biopsy should be performed in patients with advanced disease (stage III/IV), B symptoms and bony involvement or abnormal count. Bone scans are performed in patients with bone pain and/or elevation of alkaline phosphatase.

Gallium scan can be particularly helpful in identifying areas of increased uptake, which can then be reevaluated at the end of treatment. Fluorodeoxyglucose PET imaging has advantages over gallium scanning, as it is a 1-day procedure with higher resolution, better dosimetry, loss intestinal activity, and the potential to quantify disease. PET scans are being evaluated as a prognostic tool in HL, enabling therapy to be reduced in those predicted to have a good outcome.

*PET scan of the whole body:* PET scanning may identify more sites of initial disease than conventional imaging and is more accurate in detecting viable Hodgkin's lymphoma in post-therapy residual masses. Rapid early response documented by significant reduction in disease volume and PET negativity at an early stage (after one or two cycles of chemotherapy) is associated with a favorable outcome. PET scanning should be performed at baseline and a minimum of 3 weeks' postchemotherapy completion and 8–12 weeks' postradiation.

A definitive diagnosis of HL can be made only by histologic confirmation. Most frequently this is achieved with an excisional lymph node biopsy. Noninvasive needle biopsies are typically insufficient, as they do not provide material adequate to view the malignant cells, the Hodgkin and Reed-Sternberg (HRS) cells, within the context of surrounding stromal cells and nodal architecture.

Hodgkin and Reed-Sternberg cells are thought to derive from germinal center B cells that have lost their mature B-cell features, including expression of the mature B-cell marker CD20. Instead, CD30, a tumor necrosis factor (TNF) family member and transmembrane receptor, is present. One of the more frequent genetic changes in cHL is amplification of the 9p24.1 locus, leading to overexpression of the tyrosine kinase JAK2.

#### LABORATORY SALIENT FINDINGS

- ESR and acute phase reactants are elevated
- *Autoantibody phenomena:* Hemolytic anemia, idiopathic thrombocytopenic purpura
- Histological examination of lymph node
- Bone marrow examination
- Radiograph of chest
- Lymphangiography, ultrasound scanning
- CT scan of chest, abdomen, and pelvis

#### DIFFERENTIAL DIAGNOSIS

- Non-Hodgkin's disease
- Lymphoblastic leukemia
- Tuberculosis

#### MANAGEMENT (TABLE 3)

Treatment is determined largely by disease stage, presence or absence of B symptoms, and the presence of bulky nodal disease. To achieve long-term disease-free survival while minimizing treatment toxicity. Hodgkin disease is increasingly treated by chemotherapy alone and less often radiation therapy.

Most children are treated with combination chemotherapy alone or in combination with radiotherapy.

Radiation therapy alone, once given at higher doses, initially resulted in prolonged remission and

**TABLE 3:** Treatment modalities and results in Hodgkin's disease.

Stage	Treatment modality	Survival deficits (%)
I, II	Involved field RT + MOPP or COPP/ABVD 3–4 cycles	96–98
III, IV	Involved field RT + MOPP or COPP/ABVD 6 cycles	70–75

(RT: radiotherapy; MOPP: mechlorethamine, vincristine, procarbazine, and prednisolone; COPP: cyclophosphamide, vincristine, procarbazine, and prednisolone; ABVD: adriamycin, bleomycin, vinblastine, and dacarbazine)

cure rates in patients with low stage HL. However, this treatment also caused significant long-term morbidity in pediatric patients, including growth retardation, thyroid dysfunction, and cardiac and pulmonary toxicity.

The development of effective multiagent combination chemotherapy was a major milestone in the treatment of HL resulting in a complete response rate of 70–80% and cure rate of 40–50% in patients with advanced stage disease.

Management is largely determined by disease stage, patient's age, and presence of bulky nodal disease. The radiotherapy includes 3,500–4,500 cGy. The adverse reaction may be growth retardation, thyroid failure, and cardiac and pulmonary dysfunction.

Treatment in pediatric population is different in certain respects from adults. As HD is treated with a curative intention, growth and development are important issues in pediatric protocols.

## Principles of Radiotherapy

Radiotherapy has historically been an essential component of HL therapy, whereas radiotherapy is routinely incorporated into the treatment plan for adults with early-stage disease who are treated with ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) chemotherapy. Pediatric regimens omit radiotherapy for rapid or complete responders or utilize reduced radiotherapy dose and or volume strategies. The risk of radiation-induced secondary cancers, cardiovascular disease, and thyroid dysfunction throughout life is the primary driver of the different approach for pediatric HL.

- Low dose involved field radiation with, combination chemotherapy in growing children.
- For adolescents and fully grown patients with localized disease, high dose extended field radiotherapy alone remains standard treatment.
- Transposition of ovaries to midline and midline pelvic block to protect ovarian function. Testicular shield or sperm banking in male children.
- High dose radiation therapy should be avoided in young children because of late complication such as diminished growth of soft tissue and bone, hypothyroidism, gonadal dysfunction, and secondary malignancies.
- The radiotherapy includes 15–25 Gy. The adverse reaction may be growth retardation, thyroid failure, and cardiac and pulmonary dysfunction.

## Chemotherapy

Chemotherapy agents commonly used to treat children and adolescents with HL include cyclophosphamide, procarbazine, vincristine or vinblastine, prednisone or dexamethasone, doxorubicin, bleomycin, dacarbazine, etoposide, methotrexate, and cytosine arabinoside.

Superior efficacy and absence of significant toxicity have made ABVD the preferred regimen for HL.

The recommended chemotherapy includes:

- MOPP (Mechlorethamine, vincristine, procarbazine, and prednisolone)
- ABVD (Adriamycin, bleomycin, vinblastine, and prednisolone)
- High doses of anthracyclines and bleomycin should be avoided to reduce the cardiopulmonary toxicity and alkylating agents because of gonadal toxicity.

Early response to chemotherapy is currently being studied as a means of further refining therapy planning: directing those with an inadequate response toward more intensive therapy and reducing therapy for those with a rapid early response. Clinical trials by the Children's Oncology Group, have demonstrated that radiotherapy can be safely omitted for those with an adequate response to chemotherapy. Fluorodeoxyglucose PET has become an established technique for assessing response to treatment by detecting metabolic activity and distinguishing between residual disease and necrosis or fibrosis. It is important to emphasize that interim PET CT has not been validated as a predictive endpoint and its use in this setting remains investigational. Reduction in tumor mass as measured by two-dimensional area or volume on CT, or in total metabolic volume on PET may add predictive value over PET alone.

*Stages I, II and IIIA:* Four cycles of MOPP or ABVD given every 28 days. Again patient should be clinically staged, if patient has responded then two more cycles of ABVD should be given with the standard dose of the radiation therapy to the involved area, i.e., 4,000 rds.

*Stages IIB, IIIB and IV:* Six to eight total courses of MOPP alternating with ABVD given every 28 days. Six weeks after the completion of chemotherapy, all patients should be given radiation therapy to bulk disease.

## Relapse

Most relapses occur within the first 3 years after diagnosis, but relapses as late as 10 years have been reported. Relapse cannot be predicted accurately

with this disease. Poor prognostic features include tumor bulk, stage at diagnosis, extra-lymphatic disease, and presence of B symptoms. Patient who achieve an initial chemosensitive response but relapse or progress less than 12 months from diagnosis are candidates for myeloablative chemotherapy and autologous stem cell transplantation with or without the addition of radiation therapy.

Most recurrences of HL occur within 3 years after initial diagnosis, although some patients may relapse as long as 10 years after initial diagnosis. Treatment and ultimate prognosis depend on initial staging and treatment, time to relapse, extent of disease at relapse, and presence of B symptoms at relapse.

Patients with lower-risk relapses (e.g., those with late relapse of low-stage disease) may be cured with salvage chemotherapy, with or without consolidative radiotherapy. Those with primary refractory disease or very early progression (<3 months from the end of primary therapy) tend not to respond to conventional salvage therapy, and have a poor prognosis for long-term disease-free survival (30–55%). For those with higher-risk relapses or primary refractory disease who can achieve a complete remission with chemotherapy, a consolidation with myeloablative therapy followed by autologous stem cell rescue improves disease-free survival over chemotherapy alone.

Multiple salvage regimens have been used in this context, including ICE (ifosfamide, carboplatin, and etoposide), IV (ifosfamide and vinorelbine), MIED (high-dose methotrexate, ifosfamide, etoposide, and dexamethasone), and GV (gemcitabine and vinorelbine). Although these regimens have never been compared head-to-head, all have similar overall response rates. As with initial therapy, clinicians must weigh treatment intensity against toxicity, often choosing to start with the least toxic regimen and advancing to more aggressive regimens if the initial response is inadequate.

Reduced-intensity or non-myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) is under evaluation as a retrieval therapy for children with recurrent/refractory disease after autologous HSCT. Nonmyeloablative conditioning regimens most often use a nontoxic immunosuppression with the goal of establishing a graft-versus-lymphoma effect that provides a platform for adoptive cell therapy.

Treatment of the relapse includes stem cell transplantation. Other novel approaches include iodine-131 ( $^{131}\text{I}$ ) labeled antibody directed against ferritin and radionuclide yttrium.

Cyclophosphamide	: 400 mg/m <sup>2</sup> orally from day 1 to 5
Procarbazine	: 100 mg/m <sup>2</sup> orally from day 1 to 14
Vincristine	: 1.4 mg/m <sup>2</sup> intravenously daily on day 1 and 8 (weekly)
Vinblastine	: 0.1–0.15 mg/kg daily for 8 days
Prednisolone	: 40 mg/m <sup>2</sup> orally from day 1 to 14
Adriamycin	: 25 mg/m <sup>2</sup> intravenously daily for 15 days

## PROGNOSTIC FACTORS

- Stage of the disease
- *Histopathological subtype*: Risk increase from LP to NS, MC to LD
- Presence of B symptoms
- Bulky mediastinal disease
- Extensive splenic involvement
- More than five nodal sites in stage III

## LATE EFFECTS

- Hypothyroidism following RT to the neck
- Subfertility in males with alkylating agents
- Premature ovarian dysfunction with use of alkylating agents
- Adverse cardiac events following anthracycline-based regimens with or without mediastinal RT
- Pulmonary dysfunction with bleomycin
- Second malignant neoplasm

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## PRESENTING COMPLAINTS

A girl aged about 8 years was brought with the complaints of:

- Tiredness since 2 months
- Not taking food properly since 2 months
- Loss of weight since 1 month

## History of Presenting Complaints

A girl aged about 8 years was brought to hospital with history of not doing well with health and tiredness. Her mother noted that her daughter was not taking food properly. She noticed her daughter used to be lethargic and irritable. She also found that there should be loss of weight since last 2 months. She used to sit at one place and never used to play along with her friends.

## Past History of the Patient

The girl was the first sibling of nonconsanguineous marriage. She was born at full term by normal

vaginal delivery. Birth weight of child was 3 kg. There was no significant postnatal event. Child was on breast milk exclusively for 6 months. Weaning started later and child was on family food by 1 year. Her developmental milestones were normal. Her performance at school was average.

## EXAMINATION

She was moderately built and moderately nourished. She was looking very much pale. She was not interested in surroundings. Her anthropometric measurements included, the height was 124 cm (50th centile), and the weight was 16 kg (below 10th centile).

The girl was afebrile, the pulse rate was 110 per minute, and the respiratory rate was 22 per minute. The blood pressure recorded was 100/70 mm Hg. There was pallor, no edema, and no lymphadenopathy.

Bony tenderness was present at left hand and sternal tenderness was present. Per abdomen examination revealed presence of splenomegaly. Spleen was palpable about 2 cm below the costal margin. It was nontender and splenic notch was felt. There was no hepatomegaly.

## INVESTIGATION

Hemoglobin : 6.2 g/dL  
 TLC : 1,00,000 cells/cu mm  
 DLC :  $P_{68} L_{25} E_2 M_1$   
 ESR : 30 mm in the 1st hour  
 Platelet count : 2,00,000 cells/cu mm  
 Peripheral blood smear : Revealed presence of blast cells

Bone marrow examination : Showed presence of blast cells  
 X-ray of the hand : Osteolytic lesion in the humerus

## DISCUSSION

An 8-year-old girl with history of tiredness, generalized weakness, bony tenderness, pallor

### CASE AT A GLANCE

#### Basic Findings

Height : 124 cm (50th centile)  
 Weight : 16 kg (below 10th centile)  
 Temperature : 37°C  
 Pulse rate : 110 per minute  
 Respiratory rate : 22 per minute  
 Blood pressure : 100/70 mm Hg

#### Positive Findings

##### History

- Tiredness
- Loss of weight
- Lethargy

##### Examination

- Pallor
- Splenomegaly
- Sternal tenderness
- ESM
- Retinal hemorrhage

##### Investigation

- Anemia
- *Peripheral blood smear*: Presence of blast cells
- *Bone marrow*: Blast cells
- *X-ray of hand*: Osteolytic lesions

and splenomegaly was investigated. The investigation revealed leukemia. The diagnosis is supported by bony tenderness, presence of blast cells in the peripheral blood smear. Bone marrow examination revealed blast cells in marrow.

Leukemias may be defined as a group of malignant diseases in which genetic abnormalities in a hematopoietic cell give rise to an unregulated clonal proliferation of cells. The progeny of these cells have a growth advantage over normal cellular elements, because of their increased rate of proliferation and a decreased rate of spontaneous apoptosis. The result is a disruption of normal marrow function and ultimately, marrow failure. The clinical features, laboratory findings, and responses to therapy vary depending on the type of leukemia.

Leukemia is the most common form of childhood malignancy. Ninety-five percent of leukemia cases are of acute variety. Acute lymphatic leukemia (ALL) appears to be a heterogeneous disorder. There is uninhibited proliferation of lymphoblasts in bone marrow which invade blood and viscera. Acute myeloid leukemia (AML) accounts about 10–15% of childhood leukemias. The remaining subset consists of the uncommon childhood leukemias viz. chronic myeloid leukemia (CML) and juvenile myelomonocytic leukemia (JMML).

The diagnosis of ALL is often initially suspected by the presence of circulating blasts in the peripheral blood that often occurs in the setting of concomitant anemia and thrombocytopenia. Leukemia cells may also infiltrate extramedullary sites (e.g., central nervous system, testes, lymphatic system, solid organs). Patients with extramedullary lymphoid masses, but less than 25% blasts in the bone marrow, are considered to have lymphoblastic lymphoma. ALL may arise from precursor B cells (B-ALL) or T cells (T-ALL).

The incidence of childhood ALL peaks between 2 and 3 years of age and is slightly more common in males than females. The incidence of leukemia is substantially higher in white children compared to black children, with the highest rates in children of Hispanic ethnicity. With the exception of Down syndrome and rare familial leukemia predisposition syndromes, causal factors of childhood ALL remain largely unknown. Various environmental factors (e.g., viral infections, parental smoking living near power lines) potentially associated with increased risk of childhood ALL, although definitive associations have not been proven.

Exposure to very high doses of ionizing radiation, chemicals such as benzene, and certain

chemotherapies have been associated with an increased risk of AML, but not ALL.

In the clinical practice, course and prognosis of ALL is related to the type of cells involved in leukemia process.

In virtually all cases, the etiology of ALL is unknown, although several genetic and environmental factors are associated with childhood leukemia. Most cases of ALL are thought to be caused by postconception somatic mutations in lymphoid cells. However, the identification of the leukemia-specific fusion-gene sequences in archived neonatal blood spots of some children who develop ALL at a later date indicates the importance of in utero events in the initiation of the malignant process in some cases.

Although the etiology of acute leukemia is unknown, several genetic conditions and environmental agents are known to be associated with childhood leukemia. Certain inherited conditions like Down syndrome (trisomy 21), Fanconi's syndrome, Bloom syndrome, Shwachman syndrome, Klinefelter syndrome, Turner's syndrome (45,XO), neurofibromatosis, ataxia telangiectasia, severe combined immunodeficiency and Li-Fraumeni syndrome (p53 deletion) are known to predispose to leukemia. Ionizing radiation, exposure to benzene and certain drugs like alkylating agents, and epipodophyllotoxins have been incriminated in the pathogenesis of acute leukemias. Congenital leukemia (**Fig. 1**) is very rare. It is diagnosed at birth or within 1 month of life. At birth they have respiratory distress, fever, hepatomegaly, loose motions and petechiae.



**Fig. 1:** Congenital leukemia.  
(For color version see Plate 7)



It is characterized by malignant, clonal proliferation of cell precursors, i.e., blast cells. These cells will occupy and inhibit the function of bone marrow. They may circulate in blood forming leukemia deposits in any tissue.

In ALL blast cell morphology resembles precursor and lymphoid cells. In AML, the malignant cells resemble myeloid precursor.

Typing of the leukemia requires an adequate number of blast cell samples for cytogenetic studies. It should be done urgently when there are no symptoms and signs of raised intracranial tension. The diagnostic CSF is collected and if the pleocytosis is present, it indicates CNS involvement. If there are signs of raised intracranial tension then CT scan is advised.

Other rare sites of extramedullary involvement include heart, lungs, kidneys, ovaries, skin, eye or gastrointestinal tract.

## Acute Lymphoblastic Leukemia

Factors predisposing to childhood leukemia:

*Genetic conditions:*

- Down syndrome
- Fanconi anemia
- Bloom syndrome
- Diamond-Blackfan anemia
- Shwachman-Diamond syndrome
- Neurofibromatosis type 1
- Ataxia-telangiectasia
- Severe combined immune deficiency
- Paroxysmal nocturnal hemoglobinuria

*Environmental factors:*

- Ionizing radiation
- Drugs
- Alkylating agents
- Epipodophyllotoxin
- Benzene exposure

Exposure to medical diagnostic radiation both in utero and in childhood is associated with an increased incidence of ALL. In certain developing countries, there is an association between B-ALL and Epstein-Barr viral infections.

The classification of ALL has evolved from one, which was based predominantly on morphology to one, which is based on immunophenotyping, karyotyping and molecular biology techniques. For ALL, the results of immunophenotyping are used to classify the leukemia as either B-cell derived or T-cell derived. The morphologic classification (FAB classification-French American British classification) is still used by many centers, due to its ease and familiarity. It classifies the blasts as L1, L2 and L3 depending on the cell size, amount

cytoplasm and the presence of nucleoli and vacuoles.

Progenitor B-cell derived ALL constitutes 80–85% of childhood ALL. Fifteen percent are derived from T cells and 1–2% from mature B cells. Certain chromosomal abnormalities are associated with a favorable prognosis viz. t (12;21) and simultaneous presence of trisomy 4 and 10. Others like t (4;11) and the Philadelphia chromosome (9;22) and t (8;14) cannot a poor prognosis. In general, patients with hyperdiploidy (DNA index >1.16) fare better than those with hypodiploidy.

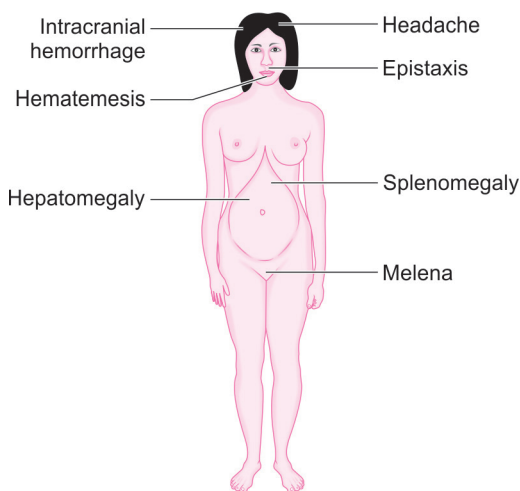
For AML, the FAB classification is widely used. However, the new classification is now gaining acceptance. According to this classification, presence of more than 20% blasts in the bone marrow is diagnostic of acute leukemia.

The presence of t (8;21), trisomy 8, and t (15;17) is associated with favorable prognosis whereas del (7) and t (4;11) are poor prognostic chromosomal abnormalities.

## CLINICAL FEATURES (FIG. 2)

Most of the clinical features are related to proliferation of lymphoblasts, displacement of erythrocytes, granulocytes and thrombocytes from the marrow, causing anemia, neutropenia and thrombocytopenia. This explains most of the clinical features of leukemia. Leukemia cells invade tissues. Immunological functions are impaired and hence these children are prone to infections.

Clinical features of acute leukemia are related to the decrease in the normal cells in the bone marrow, viz., red blood cells (RBCs), white blood cells (WBCs) and platelets, as well as the



**Fig. 2:** Clinical features.

leukemic cell infiltration of various organs (extramedullary-outside bone marrow) sites. The average duration of symptoms before diagnosis varies from 1–2 weeks to 1–2 months.

Initial symptoms may be vague like anorexia, fatigability and low-grade fever. Intermittent fever occurs as a result of cytokine induced by the leukemia itself or infections secondary leukopenia. Bone pain is severe and can wake the patient at night. Bone pain are seen especially in the pelvis, vertebral and legs. As the disease progresses, signs and symptoms of bone marrow failure become more obvious with the occurrence of pallor, fatigue, exercise intolerance, bruising, or epistaxis, as well as fever, which may be caused by infection or the disease.

In many cases of childhood ALL, production of the various types of blood cells other than lymphocytes is seriously impaired. Children may present with decreased hemoglobin and hematocrit (anemia), manifesting as pallor or fatigue. Decreased platelets (thrombocytopenia) can lead to bruising and spontaneous bleeding. Low WBC counts can lead to serious bacterial, fungal, or viral infections manifesting with fever, particularly in the context of pro-longed neutropenia or lymphopenia.

The triad of fever, pallor, and bruising is a common presentation of ALL, particularly in younger children. Some children also initially present with bone pain or refusal to walk due to leukemic infiltration of the bone marrow. Many patients with ALL present with palpable lymphadenopathy, hepatomegaly, or splenomegaly due to infiltration of organs by leukemic blasts.

Children and adolescents with ALL less commonly present with respiratory compromise due to the presence of a large anterior mediastinal mass, which is more common in patients with T-ALL. Large mediastinal masses causing respiratory distress are considered a medical emergency and often require immediate intervention. The presence of lytic bone lesions diagnosed by radiography or magnetic resonance imaging (MRI) is another rare presentation of ALL. Prior to performing a biopsy of a lytic bone lesion, a complete blood count and a careful review of the peripheral blood smear should be performed.

Organ infiltration can cause lymphadenopathy, hepatosplenomegaly, testicular enlargement, or central nervous system (CNS) involvement (cranial neuropathies, headache, seizures). Respiratory distress may be due to severe anemia or mediastinal node compression of the airways.

On physical examination, patients are usually pale with evidence of petechiae, purpura or ecchymosis.

Generalized lymphadenopathy is common either localized or generalized to cervical, axillary and inguinal regions and hepatosplenomegaly is present in 60% of patients with high tumor burden. Findings of pallor, listlessness, purpuric and petechial skin lesions, or mucous membrane hemorrhage can reflect bone marrow failure. The proliferative nature of the disease may be manifested as lymphadenopathy, splenomegaly, or, less commonly, hepatomegaly.

In patients with bone or joint pain, there may be exquisite tenderness over the bone or objective evidence of joint swelling and effusion. Nonetheless, with marrow involvement, deep bone pain may be present but tenderness will not be elicited.

Rarely, patients show signs of increased intracranial pressure that indicate leukemic involvement of the CNS. These include papilledema, retinal hemorrhages, and cranial nerve palsies. Chloroma (**Fig. 3**) is extramedullary myeloblastoma and is usually associated with myeloblastic leukemias.

Respiratory distress usually is related to anemia but can occur in patients with an obstructive airway problem (wheezing) as the result of a large anterior mediastinal mass (e.g., in the thymus or nodes). Tachypnea and respiratory distress may be present secondary to severe anemia leading to congestive cardiac failure or secondary to the



**Fig. 3:** Chloroma.

(For color version see Plate 8)

presence of a mediastinal mass leading to tracheal compression. A large mediastinal mass may also cause superior vena cava syndrome with facial edema and plethora, throbbing headache, conjunctival congestion and dilated neck veins. This problem is most typically seen in adolescent boys with T-cell ALL (T-ALL), T-ALL also usually has a higher leukocyte count.

B-lymphoblastic leukemia is the most common immunophenotype, with onset at 1–10 years of age. Testicular involvement is rarely evident at diagnosis, but prior studies indicate occult involvement in 25% of boys. There is no indication for testicular biopsy.

Bleeding tendencies like easy bruising, gum bleeding, epistaxis or petechiae and ecchymosis are common. Fever may be due to an infection like otitis media, pneumonitis or an abscess, or due to leukemia itself. Oral ulcers or thrush may be present at diagnosis. Bone and joint pains and occasionally joint swelling are common symptoms.

The course of illness is rapid. Early symptoms are nonspecific such as anorexia, irritability and lethargy. The child become markedly pale and cardiac dilatation produces hemic murmur. Hemorrhage manifestation includes epistaxis, hematemesis, melena, and intracranial bleeds. Sternal tenderness and bony pain are present. Spleen is moderately enlarged. Hepatosplenomegaly and lymphadenopathy are less marked. Because of neutropenia, phagocytosis is diminished and hence patients become more vulnerable to infection and fever. Invasion of meninges and central nervous system produces symptoms of headache, vomiting and neck rigidity. Papilledema is also encountered.

At the time of diagnosis, child with acute leukemia is often ill. This may be because of bone marrow failure, anemia, infection or bleeding. Leukemia may present as an acute emergency with life-threatening complications such as infection, hemorrhage, organ dysfunction secondary to leukocytes or signs and symptoms of superior vena cava syndrome caused by mediastinal adenopathy compressing superior vena cava.

Patient with high tumor burden can occasionally present in tumor lysis syndrome with decreased urine output and azotemia secondary to uric acid nephropathy. They may have metabolic disturbances due to tumor lysis syndrome. Deposition of leukemia cells in organs or body cavities can lead to disturbances of organ functions like superior vena caval obstruction, pleural effusion, cardiac tamponade, ascitic effusion, renal, hepatic

or splenic infiltration. They may have neurological disturbances, secondary to either intracranial bleeding, tumor deposition or metabolic disturbances.

About 5–10% patients have CNS involvement at diagnosis and present with headaches or cranial nerve palsies and nuchal rigidity. It may be associated with papilledema and other signs of raised intracranial pressure. Testes may either unilaterally or bilaterally enlarged secondary leukemic infiltration. Testicular involvement at diagnosis is extremely rare but can be present, usually with painless testicular enlargement.

Patients with acute myeloid leukemia are more likely to present with bleeding manifestations. Acute promyelocytic leukemia (APML, i.e., AML-M3) case present with disseminated intravascular coagulation due to the release of thromboplastin from the promyelocytic granules. Gum hypertrophy and skin deposits (leukemia cutis) are characteristic of AML M4/M5. Rarely patients may present with a soft tissue mass (an extramedullary myeloid cell tumor) and this may precede the leukemia in the bone marrow by several weeks.

#### GENERAL FEATURES

- Anorexia
- Irritability
- Lethargy
- Pallor
- Neutropenia

#### DIAGNOSIS

The complete blood count may reveal anemia and/or thrombocytopenia. The white cell count may be increased or decreased; in either case, it is characterized by neutropenia. Hyperleukocytosis [WBC count greater than 100,000/cu mm] is more commonly seen in ALL than AML. The peripheral blood smear may or may not reveal blasts. Often, they may be reported as atypical lymphocytes or immature cells. Coagulopathy may be present with elevated prothrombin time (PT), partial thromboplastin time (PTT) and fibrinogen degradation products.

The diagnosis of leukemia is established by a bone marrow aspiration. The presence of 25% blasts confirms the diagnosis of ALL (20% in case of AML). Rarely in case of dry tap, bone marrow biopsy may be needed.

In patients with high WBC, there may be elevation of uric acid and lactate dehydrogenase (LDH). Tumor lysis syndrome is characterized by elevated potassium, phosphorus, uric acid and

depressed calcium. In severe cases, renal function may be compromised with elevation of blood urea nitrogen and creatinine. Elevated transaminases and hyperbilirubinemia may occasionally, be present in cases of extensive liver involvement.

### Indications for Bone Marrow Examination

- Presentation suggestive of leukemia/aplastic anemia
- Sick child
- Persistent thrombocytopenia beyond 6 months
- Presence of generalized lymphadenopathy or bony tenderness
- Anemia disproportionate to the severity of bleeding
- Presence of weight loss
- Before starting corticosteroids

The diagnosis of ALL is strongly suggested by peripheral blood findings that indicate bone marrow failure. Anemia and thrombocytopenia are seen in most patients. The WBC count may be elevated or depressed, in either case it is characterized by neutropenia. Blasts may or may not be present in the peripheral blood as may be reported as atypical lymphocytes. Leukemic cells might not be reported in the peripheral blood in routine laboratory examinations. Many patients with ALL present with total leukocyte counts of  $<10,000/\mu\text{L}$ . In such cases, the leukemic cells often are reported initially to be atypical lymphocytes, and it is only on further evaluation that the cells are found to be part of a malignant clone.

When the results of an analysis of peripheral blood suggest the possibility of leukemia, the bone marrow should be examined promptly to establish the diagnosis. It is important that all studies necessary to confirm a diagnosis and adequately classify the type of leukemia be performed, including bone marrow aspiration and biopsy, flow cytometry, cytogenetics, and molecular studies.

Acute lymphatic leukemia is diagnosed by a bone marrow evaluation that demonstrates  $>25\%$  of the bone marrow cells as a homogeneous population of lymphoblasts bone marrow aspiration smears confirm the diagnosis when more than 30% blasts are present ( $>20\%$  for AML by the WHO classification).

Initial evaluation also includes CSF analysis, including cytology is necessary for staging. If lymphoblasts are found and the CSF leukocyte count is elevated, overt CNS or meningeal leukemia is present. This finding reflects a worse stage and indicates the need for additional CNS and systemic therapies.

Morphology along with cytochemistry can accurately diagnose about 80% acute leukemias. Immunophenotyping is useful for further subtyping according to the lineage and for tailoring treatment and for prognostication. Rarely a bone marrow biopsy is necessary for adequate tissue to rule out other causes.

Biochemical evaluation including liver and renal function tests, serum LDH, uric acid, electrolytes and calcium, phosphorus and magnesium levels should be performed to establish baseline organ function and to rule out tumor lysis syndrome.

Serology for HIV, hepatitis B and C and EBV and CMV should be performed at diagnosis. Coagulation profile with PT, PTT, fibrinogen level and FDP should be done to rule out DIC.

Chest X-ray may reveal a mediastinal mass, more often, in T-cell ALL, hepatosplenomegaly and occasionally nephromegaly may be documented by a sonography.

#### LABORATORY SALIENT FINDINGS

- Anemia, neutropenia, thrombocytopenia
- Peripheral blood smear: elevated lymphoblasts, tear drop RBCs, decreased platelet counts
- Decreased hemoglobin
- Uric acid and lactate dehydrogenase (LDH) are elevated
- Bone marrow examination: leukemic blast cells
- Chest X-ray
- Abdominal ultrasonography
- Plain X-ray of long bones

### DIFFERENTIAL DIAGNOSIS

- Idiopathic thrombocytopenic purpura
- Scurvy
- Rheumatoid arthritis
- Lymphoma
- Histiocytosis

The differential diagnosis of ALL several benign and malignant conditions, viral infection-induced cytopenias are the most common conditions, which mimic leukemia, infectious mononucleosis, cytomegalovirus infection and a host of other viral infections may present with fever and lymphadenopathy along with anemia, thrombocytopenia and/or neutropenia with atypical lymphocytosis.

Immune thrombocytopenia presents with sudden onset of thrombocytopenia with petechiae, purpura and ecchymosis in an otherwise well child. The presence of atypical features like fever, lymphadenopathy or anemia may warrant a bone marrow examination to rule out leukemia.

Drug-induced cytopenias can be suspected by, a detailed history and withdrawal of the offending drug usually leads to recovery of the concerned cell lines. Bone marrow failure syndromes, myelodysplastic syndromes and hypoplastic/aplastic anemia usually have a long-standing history and need a bone marrow biopsy for confirmation. Some collagen vascular disorders like rheumatoid arthritis and systemic lupus erythematosus can present with symptoms of leukemia, Langerhans cell histiocytosis with or without marrow involvement is another common differential.

Malignant conditions that mimic acute leukemia include metastases from solid tumors like neuroblastoma and rhabdomyosarcoma and marrow involvement in non-Hodgkin lymphoma (NHL).

The differential diagnosis of acute leukemia includes other hematologic malignancies like chronic myeloid leukemia, juvenile myelomonocytic leukemia, chronic myeloid leukemia in blast crisis or lymphoma evolving to leukemic phase. Bone marrow failure secondary to marrow infiltration by metastatic deposits in neuroblastoma, rhabdomyosarcoma and Ewing's sarcoma can occasionally mimic acute leukemia.

## PROGNOSTIC FACTORS

The combination of age and WBC is currently used for initial risk group allocation in patients with B-ALL. Standard risk B-ALL is defined as age >1 and <10 years and a WBC of <50,000/ $\mu$ L, while high-risk B-ALL is defined as age 2–10 years and/or initial WBC 50,000/ $\mu$ L. Children with CNS positivity are also generally considered high risk. Hepatosplenomegaly and other extramedullary involvement at diagnosis have no independent prognostic significance. CNS involvement of leukemia is a less favorable prognostic factor, and testicular involvement with leukemia in males is also considered high risk.

## TREATMENT

Modern treatment for childhood ALL consists of multiagent chemotherapy administered in several phases: induction, consolidation, intensification, and maintenance phases of therapy. The induction phase of treatment generally lasts 1 month, and over 95% of children achieve a remission at the end of this phase. The next phases of treatment (consolidation and intensification) are designed to intensify systemic and CNS-directed therapy to eradicate any residual disease. The final and longest phase of treatment (maintenance) is

designed to prevent disease recurrence. In general, treatment is 2–3 years in duration. Some earlier ALL studies treated boys for longer than girls because male gender was associated with inferior outcomes.

The management of acute leukemia is intense and prolonged. It needs the combines efforts of the pediatric oncologist, the radiotherapist, the dietician, the psychologist and the medical social workers to treat these children.

## Treatment of Acute Lymphatic Leukemia

**Chemotherapy:** It consists of induction of remission and consolidation to attain disease control. Maintenance treatment is to avoid recurrence of leukemia in bone marrow and CNS prophylaxis.

**Induction of remission:** Initial therapy, termed *remission induction*, is designed to eradicate the leukemic cells from the bone marrow. During this phase, therapy is given for 4 weeks and consists of vincristine weekly a corticosteroid such as dexamethasone or prednisone, and usually a single dose of a long-acting, pegylated asparaginase preparation. Patients at higher risk also receive daunomycin at weekly intervals. Within approach, 98% of patients are in *remission*, as defined by <5% blasts in the marrow and a return of neutrophil and platelet counts to near normal levels after 4–5 weeks of treatment and at least once more during induction.

The drugs used are vincristine 15 mg/m<sup>2</sup>, prednisolone 60 mg/m<sup>2</sup>, Adriamycin 20 mg/m<sup>2</sup>/week, for 4–5 weeks. L-asparaginase 10,000 U/m<sup>2</sup>/three times/week for 2 weeks. The total induction treatment is 4–6 weeks. If normal bone marrow is not achieved, treatment can be carried out for two additional weeks.

**Central nervous system prophylaxis** is carried out weekly by intrathecal injection of methotrexate for 5–6 weeks followed by every 8 weeks of intrathecal injection for maintenance therapy period. Patients with CNS involvement may sometimes require cranial radiation 1800–2000 rads and intrathecal methotrexate. This is combined with hydrocortisone (12 mg/m<sup>2</sup>) given as triple intrathecal therapy. This is followed by CNS therapy.

**Consolidation chemotherapy:** The second phase of treatment, consolidation, focuses on intensive *CNS therapy* in combination with continued intensive systemic therapy in an effort to prevent later CNS relapses. CNS therapy consists of cranial irradiation and intrathecal chemotherapy.



The concept of CNS preventive therapy is based on the assumption that undetectable CNS leukemia is present at diagnosis. Cranial irradiation with intrathecal MTX has been in use as CNS preventive therapy. This causes significant adverse effect on neurocognitive function in some survivors. Hence, most western protocols reserve cranial irradiation for patients with CNS disease at presentation and those who are at high risk for CNS relapse. Children younger than 3 years of age are given high dose chemotherapy using cytosine arabinoside, in an attempt to prevent radiation to the developing brain.

Intrathecal chemotherapy is given repeatedly by lumbar puncture. The likelihood of later CNS relapse is thereby reduced to <5%, from historical incidence as high as 60%. A small percentage of patients with features predict a high risk of CNS relapse may receive irradiation to the brain in later phases of therapy. This includes patients who, at the time of diagnosis, have lymphoblasts in the CSF and either an elevated CSF leukocyte count or physical signs of CNS leukemia, such as cranial nerve palsy.

Consolidation chemotherapy follows CNS therapy and is aimed at decreasing the leukemic burden further. Drugs used include vincristine, cyclophosphamide, and daunorubicin and cytosine arabinoside.

Consolidation therapy is carried out by cyclophosphamide, L-asparaginase, or multiple drug combinations. These include newer agents such as VP-16, VM-26 and high dose cytosine arabinoside, i.e., 1–2 g/m<sup>2</sup>.

Subsequently, many regimens provide 14–25 weeks therapy, with the drugs and schedules used varying depending on the risk group of the patient. This period of treatment is often termed and includes phases of aggressive treatment (delayed *intensification*) as well as relatively non-toxic phases of treatment (interim maintenance), multiagent chemotherapy, including such medications as cytarabine, methotrexate, asparaginase, and vincristine, is used airily, these phases to eradicate residual disease.

**Maintenance chemotherapy:** Finally, patients enter the *maintenance* phase of therapy, which lasts for 2–3 years, depending on the protocol used. Patients are given daily mercaptopurine and weekly oral methotrexate, usually with intermittent doses of vincristine and a corticosteroid.

Maintenance chemotherapy using mercaptopurine and methotrexate is continued for 2 years in order to eradicate dormant leukemia cells.

Maintenance therapy is done with 6-mercaptopurine at a dose of 50–75 mg/m<sup>2</sup>/day and methotrexate in dose of 20 mg/m<sup>2</sup>/week. The period of maintenance therapy is 130 weeks of continuous remission. Absolute neutrophil count should be maintained between 750 and 1500 cells/cu mm. Prophylactic treatment with cotrimoxazole helps to reduce infection.

Complete response can be achieved in 92% of the patients at the end of induction. Relapse of disease occurs in 25–30% patients treated with this protocol at various centers. Most relapses occur during maintenance and within the first 6 months of completion of therapy.

A small number of patients with particularly poor prognostic features, such as those with induction failure or extreme hypodiploidy, may undergo bone marrow transplantation during the first remission.

Adolescents and young adults with ALL have an inferior prognosis compared to children younger than 15 years old. They often have adverse prognostic factors and require more intensive therapy. Patients in this age group have a superior outcome when treated with pediatric as opposed to adult treatment protocols. Although the explanation for these findings may be multifactorial, it is important that these patients be treated with pediatric treatment protocols, ideally in a pediatric cancer center.

## Treatment of Acute Myeloid Leukemia

Induction chemotherapy for AML consists of aggressive multiagent protocols (**Table 1**). An anthracycline (daunorubicin or idarubicin) is used in combination with cytosine arabinoside, given over 7–10 days. The resultant myelosuppression takes about 3–4 weeks to recover. About 70% patients achieve remission at the end of induction chemotherapy. Postremission treatment consists of two courses of high-dose chemotherapy using cytosine arabinoside. About 3–4 months of maintenance chemotherapy is recommended in children.

The IOSG (Indian Oncology Study Group) protocol (**Table 2**) has given good results in children with AML. Acute promyelocytic (APML) is characterized by the T(15:17) involving the retinoic acid receptor A (RAR- $\alpha$ ). The use of ATRA (all transretinoic acid) causes the differentiation of the promyelocytes leading to their maturation with resolution of the coagulopathy. Its use in combination with chemotherapy like anthracycline leads to complete remission.

TABLE 1: Protocol for acute lymphatic leukemia (ALL).

Cycle	Chemotherapy	Dose and schedule
Induction 1	Prednisone Vincristine Methotrexate L-asparaginase Daunorubicin	40 mg/m <sup>2</sup> PO days 1–28 1.4 mg/m <sup>2</sup> IV days 1, 8, 15 and 22 12 mg IT, days 1, 8, 15 and 22 6000 µ/m <sup>2</sup> IM qod x 10 doses, days 2, 20 30 mg/m <sup>2</sup> IV days 8, 15 and 29
Induction 2	Mercaptopurine Cyclophosphamide Methotrexate Cranial radiation	75 mg/m <sup>2</sup> PO daily days 1–7 and days 15–21 750 mg/m <sup>2</sup> IV days 1–15 12 mg/m <sup>2</sup> IT days 1, 8, 15 and 22 180 cGy daily x 10 days (total 1800 cGy)
Repeat induction (R1)	Same as 1	Doses and schedule as per 1
Consolidation (C)	Cyclophosphamide Vincristine Mercaptopurine Cytarabine Daunorubicin	750 mg/m <sup>2</sup> IV day 1 1.4 mg/m <sup>2</sup> IV days 1 and day 15 75 mg/m <sup>2</sup> PO daily days 1–7 and days 15–21 100 mg/m <sup>2</sup> SC every 12 hours x 6 doses on days 1–3 and days 15–17 30 mg/m <sup>2</sup> IV days 15
Maintenance (M, six cycles)	Prednisone Vincristine Daunorubicin L-asparaginase Methotrexate  Mercaptopurine	40 mg/m <sup>2</sup> PO days 1–7 1.4 mg/m <sup>2</sup> IV on day 1 30 mg/m <sup>2</sup> IV on day 1 6000 µ/m <sup>2</sup> IM days 1, 3, 5 and 7 15 mg/m <sup>2</sup> PO once a week. Missing every 4th for a total of 12 weeks. Begin on day 15  75 mg/m <sup>2</sup> PO daily, 3 weeks out of every 4 for total of 12 weeks. Begin on day 15

TABLE 2: IOG protocol for acute myeloid leukemia (AML).

<b>Induction</b>
<ul style="list-style-type: none"><li>Daunorubicin (60 mg/m<sup>2</sup>/day x 3 days) or idarubicin (12 mg/m<sup>2</sup>/day x 3 days)</li><li>Cytosine arabinoside (100 mg/m<sup>2</sup>/day as 24 hours continuous infusion x 7 days)</li></ul>
<b>Consolidation I</b>
High dose cytosine arabinoside (1.5 g/m <sup>2</sup> /dose every 12 hourly x 5 days)
<b>Consolidation II</b>
Same as consolidation I
<b>Maintenance x 4 cycles</b>
<ul style="list-style-type: none"><li>Daunorubicin (45 mg/m<sup>2</sup>/day x 1 day)</li><li>Cytosine arabinoside (100 mg/m<sup>2</sup>/every 12 hourly SC x 5 days)</li></ul>

Maintenance therapy with ATRA improves long-term disease free survival. Arsenic trioxide, alone or in combination with ATRA has also produced excellent response rates in APML patient.

Supportive Care

Supportive care is extremely important in the treatment of acute leukemias. This includes blood component therapy and aggressive management

of infectious complications. Packed red blood cell transfusions are indicated to maintain hemoglobin over 8 g/dL in well children and over 10 g/dL in patients with fever and infection. Platelet transfusions are indicated if platelet count is less than 10000/cu mm or in the case of overt bleeding, especially inpatients with fever and infection. Every episode of febrile neutropenia should be treated aggressively with broad-spectrum antibiotics after drawing blood cultures.

All patients should receive prophylaxis for *Pneumocystis carinii* pneumonia with cotrimoxazole and for fungal infections with clotrimazole. Maintenance of oral and perianal hygiene reduces the risk of infections to a significant extent. The use of hematopoietic growth factors (GCSF and GMCSF) reduces the period of neutropenia but are expensive and do not improve the overall outcome of the patients. The use of long-term indwelling venous access devices, which allows for easy blood collections and for administration of intravenous medication and blood products makes and treatment of acute leukemias less painful and more patient friendly.

The successful therapy of ALL is a direct result or intensive and often toxic treatment. However, such intensive therapy can incur substantial academic, developmental, and psychosocial costs

for children with considerable financial costs and stress for their families. Both long-term and acute toxicity effects can occur. An array of cancer care professionals with training and experience in addressing the myriad of problems that can arise is essential to minimize the complications and achieve an optimal outcome.

Infants with AML often present with CNS or skin involvement and have a subtype known as acute myelomonocytic leukemia. The treatment may be the same as that for older children with AML, with similar outcome. Meticulous supportive care is necessary because of the young age and aggressive therapy needed in these patients.

Several new biological agents, including tyrosine kinase inhibitors and immunotoxins, are currently in various stages of research.

### Bone Marrow Transplantation

Bone marrow transplantation or stem cell transplantation is indicated in patients with acute leukemia in first remission only if associated with very high-risk factors, viz., ALL with t(9:22) or t(4:11) or in AML with monosomy 5 or 7, t(9:22) or t(6:9).

Patients whose blasts contain certain chromosomal abnormalities, hypodiploidy (<44 chromosomes) and patients very slow response to therapy may have a better cure rate with early hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA)-DR-matched sibling donor, or a matched unrelated donor, than with the intensive chemotherapy alone. HSCT cures about 50% of the patients who relapse, provided that a second remission is achieved with chemotherapy before transplant.

Any patient with acute leukemia, who relapses, needs a transplant while in second remission in an attempt to achieve cure.

### *Treatment of Relapse*

Despite numerous advances in the treatment and supportive care for children with ALL, 2–3% will die of infectious or other toxic complications, 1% will develop a second malignant neoplasm, and 10–15% will relapse. Recurrent or relapsed ALL remains a significant challenge, as fewer than 50% of patients will survive long-term. Relapse can occur in the bone marrow or extramedullary sites, with CNS and testes being most common, or in both locations. The most important prognostic-factors for recurrent ALL are the site and timing of the recurrence relative to the initial diagnosis. In general, isolated bone marrow relapse carries

a worse prognosis compared to extramedullary or combined relapse. Early relapse (<36 months from initial diagnosis) has a worse outcome than late relapse. Relapses of T-ALL are particularly challenging to treat and have very few long-term survivors.

The major impediment to a successful outcome is relapse of the disease. Outcomes remain poor among those that relapse, with the most important prognostic indicators being time from diagnosis and the site of relapsed disease, in addition, other factors, such as immunophenotype (T-ALL worse than ALL) and age at initial diagnosis, have prognostic significance.

Relapse occurs in the bone marrow in 15–20% of patients with ALL and carries the most serious implications, especially if it occurs during or shortly after completion of therapy. Intensive chemotherapy with agents not previously used in the patient followed by allogeneic stem cell transplantation can result in long-term survival for some patients with bone marrow relapse.

The incidence of CNS relapse has decreased to <5% since introduction of preventive CNS therapy. CNS relapse may be discovered at the time of a routine lumbar puncture in the asymptomatic patient. Symptomatic patients with relapse in the CNS usually present with signs and symptoms of increased intracranial pressure and call present with isolated cranial nerve palsies. The diagnosis is confirmed by demonstrating the presence of leukemic cells in the CSF. The treatment includes intrathecal medication and cranial or craniospinal irradiation. Systemic chemotherapy also must be used, because these patients are at high risk for subsequent bone marrow relapse. Most patients with leukemic relapse confined to the CNS do well especially those in whom the CNS relapse occurs longer than 18 months after initiation of chemotherapy.

Testicular relapse occurs in less than 2% of boys with ALL, usually after completion of therapy. Such relapse occurs as painless swelling of 1 or both testes. The diagnosis is confirmed by biopsy of the affected testis. Treatment includes systemic chemotherapy and possibly local irradiation. A high proportion of boys with a testicular relapse can be successfully retreated and the survival rate of these patients is good.

### PROGNOSIS

Two most important prognostic factors are age at diagnosis and initial WBC count. Prognosis is unfavorable in children with age below 2 years and above 8 years. Significant hepatosplenomegaly,

lymphadenopathy, mediastinal enlargement, central nervous system, testicular involvement carry poor prognosis. Prognosis is poor if WBC count is more than 50,000 cell/cu mm hypogammaglobinemia, hypodiploidy.

Acute lymphatic leukemia is a heterogenous disease and prognosis depends on the subtype, the tumor burden at presentation, the associated cytogenetic abnormality, the ploidy, and most importantly, the response to treatment. Early clearance of blasts from the peripheral blood (day 7 absolute blast counts) after initiation of treatment and evidence of bone marrow remission on day 14 of induction therapy has been associated with a very good prognosis.

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## PRESENTING COMPLAINTS

An 18-month-old boy was brought with the complaints of:

- Swelling in abdomen since 2 months
- Loose motion since 15 days
- Vomiting since 3 days

## History of Presenting Complaints

An 18-month-old boy was referred by a general practitioner for evaluation of swelling in the abdomen. According to the mother, his son was taken to the doctor for treatment of loose motion and vomiting. During the examination doctor had found a mass in the upper abdomen. Hence he referred the boy to a hospital for evaluation of the mass. Mother also revealed the history of the presence of swelling in the child.

### CASE AT A GLANCE

#### Basic Findings

Height	: 84 cm (90th centile)
Weight	: 10.5 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 120 per minute
Respiratory rate	: 32 per minute
Blood pressure	: 70/50 mm Hg

#### Positive Findings

##### History

- Mass per abdomen
- Loose motions
- Sweating

##### Examination

- Mass per abdomen
- Sign of moderate dehydration

##### Investigation

- Serum electrolytes:  
Na—110 mEq/L  
K—3 mEq/L  
Cl—90 mEq/L
- Urinary VMA: Increased
- Excretory urogram: Showed displacement of left kidney
- Biopsy: Neuroblast cells, large amount of cytoplasm

## Past History of the Patient

He was the only sibling of consanguineous marriage. He was born at full term with normal vaginal delivery. The baby cried immediately after the delivery. The birth weight of the child was 3 kg, the length of the child was 51 cm, and the head circumference was 35 cm. There was no significant postnatal history except for transient tachypnea of the newborn which settled by itself without any treatment. He was on breast milk exclusively for 4 months. Weaning started with cereals and fruits. His developmental milestones were normal. According to mother, his son was suffering mainly from loose motion and vomiting for which he was seeking treatment by his family doctor.

## EXAMINATION

The child was moderately built and nourished. The child was irritable and signs of moderate dehydration were present. Anthropometric measurements included, the height was 84 cm (90th centile), the weight was 10.5 kg (50th centile), and the head circumference was 48 cm. Anterior fontanelle was normal. The heart rate was 120 per minute and the respiratory rate was 32 per minute. The blood pressure recorded was 70/50 mm Hg. There was no pallor, no icterus, no lymphadenopathy, and no cyanosis.

Per abdomen examination revealed presence of mass in epigastric region. The mass measured about 3 cm × 2 cm. The consistency was firm. The mass was nontender. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 7,600 cells/cu mm
Serum electrolytes	: Na—110 mEq/L K—3 mEq/L Cl—90 mEq/L
Urinary VMA	: 20 mg/day (Normal range: 2–10 mg/day)



Excretory urogram	: Showed displacement of left kidney downward and slightly lateral suprarenal mass
Biopsy	: Showed primitive neuroblast cells, cytoplasmic process rosettes and central fibrillar material
CT scan of abdomen and chest	: Normal

## DISCUSSION

Neuroblastomas are embryonal cancer of the peripheral sympathetic nervous system with heterogeneous clinical presentation and course, ranging from tumors that undergo spontaneous regression to very aggressive tumors unresponsive to very intensive multimodal therapy. Neuroblastoma and related neoplasms arise from those neural crest cells which differentiate in cells of the sympathetic ganglia and adrenal medulla. Because neuroblastoma arises from any site along the sympathetic chain, the location of primary tumor at diagnosis are varied and changed with age.

The most common sites are adrenal, sympathetic chain, retroperitoneal area, posterior mediastinum, and cervical area.

Neuroblastoma, a tumor of the sympathetic nervous system, is the most common extracranial solid tumor of childhood. Neuroblastoma is a clinically heterogeneous disease, as infants with metastatic disease may experience complete tumor regression without therapy, while other children may experience relentless disease progression despite modern multimodality therapy. Current risk classification schemes used clinical, histological, and genomic features at diagnosis to predict tumor behavior and to assign patients to an appropriate treatment regimen based on risk of recurrence. Children with lower risk disease are spared unnecessary therapies yet still achieve excellent outcomes. Nevertheless, outcome remains poor for patients classified as high risk.

## EPIDEMIOLOGY

Neuroblastoma is the most common extracranial solid tumor in children and the most commonly diagnosed malignancy in infants. It accounts for 7–10% of the childhood cancer. The etiology is unknown. Occasionally, it is congenital with metastasis to the placenta. Neuroblastoma accounts for >15% of the mortality from cancer in children.

The median age of children at diagnosis of neuroblastoma is 2 years, and 90% of cases are diagnosed by 5 years of age. The incidence is slightly higher in boys and in whites.

It is unique with high rate of spontaneous regression. Neuroblastoma in situ is related to nodular clusters of the neuroblasts. There is an association with neurofibromatosis, Hirschsprung's disease, heterochronic fetal hydantosis and fetal alcohol syndrome and Friedrich's ataxia. Rearrangement or deletion of the short arm of chromosome number 1 has been found.

## PATHOLOGY

Neuroblastoma tumors, which are derived from primordial neural crest cells, form a spectrum with variable degrees of neural differentiation, ranging from tumors with primarily undifferentiated small round cells (neuroblastoma) to tumors consisting of mature and maturing Schwannian stroma with ganglion cells (ganglioneuroblastoma or ganglioneuroma).

In gross pathology, this tumor is seen as a firm gray mass. Hemorrhage into the tumor produces variegated maroon color often with necrosis and calcification. Most tumors contain primitive neuroblastoma cells. Some tumors have large amount of cytoplasm, with cytoplasmic process, rosettes and central fibrillar material.

Neuroblastoma is one of the small blue round cells tumors of childhood (others are Ewing's sarcoma, non-Hodgkin's lymphoma, primitive neuroectodermal tumor and rhabdomyosarcoma). The typical neuroblastoma is composed of small, uniform cells with hyperchromatic nuclei and scanty cytoplasm that may form rosette pattern. The presence of neuritic processes (neutrophil) and Homer Wright pseudorosettes helps to distinguish neuroblastoma from other round cell tumors. The fully differentiated, benign counterpart of neuroblastoma is the ganglioneuroma, which is composed of mature ganglion cells, neutrophils and Schwann cells. Ganglioneuroblastoma has features intermediate to those of the other two.

The prognosis of children with neuroblastoma varies with the histologic features of the tumor, and prognostic factors include the presence and amount of Schwannian stroma, the degree of tumor cell differentiation, and the mitosis-karyorrhexis index.

## PATHOGENESIS

The etiology of neuroblastoma in most cases remains unknown. Familial neuroblastoma

accounts for 1–2% of all cases, is associated with a younger age at diagnosis, and has been linked to mutations in the *Phox2B* and *ALK* genes. The *BARD1* gene has also been identified as a major genetic contributor to neuroblastoma risk. Neuroblastoma is associated with other neural crest disorders, including Hirschsprung's disease, central hypoventilation syndrome, and neurofibromatosis type I, and potentially congenital cardiovascular malformations. Children with Beckwith-Wiedemann syndrome and hemihypertrophy also have a higher incidence of neuroblastoma.

Genetic characteristics of neuroblastoma tumors that are of prognostic importance include amplification of the *MYCN* (*N-myc*), proto-oncogene and tumor cell DNA content, or ploidy. Amplification of *MYCN* is strongly associated with advanced tumor stage and poor outcomes. Hyperdiploidy confers better prognosis if the child is younger than 1 year of age at diagnosis. Other chromosomal abnormalities, including loss of heterozygosity (LOH) of 1p, 11q, and 14q, and gain of 17q, are commonly found in neuroblastoma tumors and are also associated with worse outcomes.

Neuroblastoma arises from sympathetic neuroblasts, and neuronal differentiation is often seen on histologic evaluation. Some tumors undergo spontaneous or therapy-induced differentiation, suggesting that the malignant behavior of these cells may be maintained in part by a failed differentiation program. The factors responsible for regulating differentiation or regression are not well understood but may involve neurotrophin signaling, as neurotrophin pathways play a key role in the development of the sympathetic nervous system.

## CLINICAL FEATURES (FIG. 1)

Clinical features are related to the localization of sympathetic nervous system and site of metastasis. Symptoms will be different if the tumor is located in the neck or in the pelvis. The most common sites of primary lesion are adrenal gland, paravertebral glands, retroperitoneum, posterior mediastinum, pelvis, and cervical area.

Clinical features vary with primary site of malignant disease and neuroendocrine functions of the tissue. Neuroblastoma may develop at any site of sympathetic nervous system tissue. Approximately half of neuroblastoma tumors arise in the adrenal glands, and most of the remainder originate in the paraspinal sympathetic ganglia.

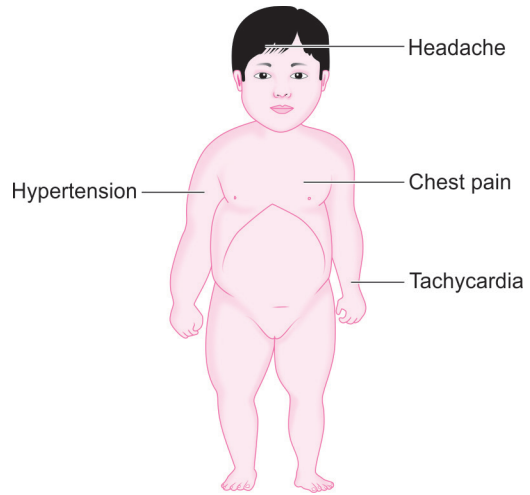


Fig. 1: Clinical features.

Metastatic spread, which is more common in children older than 1 year of age at diagnosis, occurs via local invasion or distant hematogenous or lymphatic routes. The most common sites of metastasis are the regional or distant lymph nodes, long bones and skull, bone marrow, liver, and skin. Lung and brain metastases are rare, occurring in >3% of cases.

Neuroblastoma has polymorphic symptoms. This is because of numerous sites of primary tumor and to the patterns in widespread metastasis. There are tumor associated metabolic disturbances.

The signs and symptoms of neuroblastoma depends on the tumor site and extent of disease, and the symptoms of neuroblastoma can mimic many other disorders, a fact that can result in a delayed diagnosis.

Metastatic disease can cause a variety of signs and symptoms, including fever, irritability, failure to thrive, bone pain, cytopenias, bluish subcutaneous nodules, orbital proptosis, and peri-orbital ecchymoses. Localized disease can manifest as an asymptomatic mass or can cause symptoms because of the mass itself, including spinal cord compression, bowel obstruction, and superior vena cava syndrome. It has predilection for metastasis to skull especially to sphenoid bone and retrobulbar tissue causing periorbital ecchymosis and proptosis.

Metastatic sites are bone, bone marrow, lymph nodes, liver, and subcutaneous tissue.

The primary tumor is usually in the abdomen. The mass usually is in the upper abdomen as it will be mainly in adrenal (40%). It presents as a firm, irregular and nontender mass. It accounts 25% of

paraspinal ganglion. In posterior mediastinum, the tumor is usually asymptomatic and discovered on chest X-ray accidentally. The primary tumor extend beyond midline, margins are often poorly defined.

Hemorrhage into the enlarging tumor is common and may even produce pallor and hypotension. Hepatic enlargement and ascites will occur with hepatic involvement.

Children with neuroblastoma can also present with neurologic signs and symptoms, Neuroblastoma originating in the superior cervical ganglion can result in *Horner syndrome (unilateral ptosis, miosis and anhidrosis)*. Paraspinal neuroblastoma tumors can invade the neural foramina, causing spinal cord and nerve root compression. It can develop either intraspinally or extraspinally. It can either extend on dumbbell fashion between intervertebral foramen. This causes cord compression, back pain, sphincter dysfunction, paraplegic or quadriplegic and gait disturbances.

Neuroblastoma can also be associated with a paraneoplastic syndrome of autoimmune origin, termed *opsoclonus-myoclonus-ataxia syndrome*, in which patients experience rapid, uncontrollable jerking eye and body movements, poor coordination and cognitive dysfunction. Some tumors produce catecholamines that can cause increased sweating and hypertension, and some release vasoactive intestinal peptide, causing a profound secretory diarrhea. Children with extensive tumors can also experience tumor lysis syndrome and disseminated intravascular coagulation. Child may present with paresis, paralysis and bowel, and bladder dysfunction.

Encephalopathy involving the cerebellum produces the syndrome called opsomyoclonus. It is characterized by progressive ataxia, titubation of head, myoclonic jerks and chaotic conjugate jerking movements of the eyes. With progression, secretory diarrhea occurs due to vasointestinal peptide secretion by tumor. This will be associated with atonic bladder.

There will be extreme loss of potassium. It may occur as a result of overproduction of vasoactive intestinal peptide. Hypertension is very rare with neuroblasts. It is common with pheochromocytoma. Episodes of unexplained sweating and flushing have been reported due to catecholamine release.

It may extend to surrounding tissues by local invasion or to the regional lymph nodes by lymphatics. Hematogenous spread most frequently involves liver, bone marrow, and skeleton. Metastasis to the brain is rare.

Subcutaneous nodules are bluish in color and associated with erythematous flush followed by blanching when compressed, secondary to catecholamine release.

ESSENTIAL DIAGNOSTIC POINTS

- Abdominal pain, bone pain, irritability
- Anorexia, weight loss, fatigue, fever
- Abdominal mass adenopathy, hepatomegaly
- Periorbital ecchymosis, proptosis
- Skull masses, subcutaneous nodules, spinal cord compression

GENERAL FEATURES

- Anorexia
- Listlessness
- Anemia
- Loss of weight
- Cough

DIAGNOSIS

Neuroblastoma is usually discovered as a mass or multiple masses on plain radiography, computed tomography (CT), or magnetic resonance imaging (MRI). The mass often contains calcification and hemorrhage that can be appreciated on plain radiography or CT. Prenatal diagnosis of neuroblastoma on maternal ultrasound scans is sometimes possible. Tumor markers, including catecholamine metabolites homovanillic acid (HVA) and vanillylmandelic acid (VMA), are elevated in the urine of approximately 95% of cases and help to confirm the diagnosis. A pathologic diagnosis is established from tumor tissue obtained by biopsy.

Evaluation of Patient

Evaluations for metastatic disease should include CT or MRI of the chest and abdomen, bone scan to detect cortical bone involvement, and at least two independent bone marrow aspirations and biopsies to evaluate for marrow disease. *Iodine-123 metaiodobenzylguanidine (<sup>123</sup>I-MIBG)* studies should be used when available to better define the extent of disease.

- *Primary site:*
  - X-ray, USG, CT scan, MRI
  - 24 hours-urinary VMA
- *Metastatic disease:*
  - Bone marrow aspiration and trephine biopsy
  - Technetium bone scan

For the abdominal tumor, CT scan will be helpful. Radiography of abdomen and excretory

urography are done. Helpful findings include calcification or displacement of renal collecting system or of the ureter.

CT scan shows mixed tissue density including both solid and cystic components. The cystic area is either hemorrhagic or necrotic in tumor. Metrizamide myelography along with CT may be required to define the extent of intraspinal extension of the disease.

A standard evaluation to determine the extent of disease is performed at diagnosis. CT scan or MRI of the neck, chest, abdomen, and pelvis are used to evaluate the primary tumor, and to detect regional or distant disease. MRI is superior to CT in evaluating paraspinal mass lesions for intraforaminal extension and spinal cord compression.

Bone scan shows periosteal lytic lesion in skull. It is helpful in defining the extent of metastatic disease. Bone marrow aspiration or biopsy should be performed for staging in all patients. Bone marrow disease is assessed via bilateral bone marrow aspirates and trephine biopsies. Immunohistochemistry is now widely used to confirm the presence of tumor in the marrow. Molecular assays that detect neuroblastoma cells in bone marrow are highly sensitive. However, the use of these assays has not been incorporated into routine clinical practice at this time.

The specific diagnostic feature is the elevated levels of catecholamines in the urine. Increased levels of dihydroxyphenylalanine (DOPA), dopamine, norepinephrine, normetanephrine, HVA, or VMA are present. This provides an ancillary diagnostic test, as well as a means to follow disease activity. The two enzymes primarily responsible for the catabolism of catecholamines are catechol-O-methyltransferase and monoamine oxidase. DOPA and dopamine are converted primarily to HVA, whereas norepinephrine and epinephrine are converted primarily to VMA. Both urinary VMA and HVA should be normalized for age and for urinary creatinine.

## Imaging

Conventional radiography often reveals mediastinal widening in stippled calcification in an abdominal tumor. A complete body bone scan is useful in detecting bone metastasis and is necessary for staging. Metastatic to bone appear irregular and lytic, periosteal reaction, and pathological fracture.

Ultrasound, CT scan, and MRI all help to delineate the primary tumor and detect metastasis. CT scan helps to know extension of primary

lesion, presence metastasis in lymph node and liver. MRI is helpful to detect presence spinal cord involvement and that appear involve neural foramina.

The methyl iodobenzylguanidine (MIBG) scintigraphy scan is a radiolabeled, specific and very sensitive method for evaluation and follow-up of primary and metastatic disease. Recent reports also suggest its very useful therapeutic role in the treatment of advanced and relapsed disease.

Myelography is very important in the evaluation of primary or metastatic spinal disease and performed early can diagnose the exact location and site of lesions causing impending motor weakness of the limbs. However, safer modes of investigations (e.g., MRI) are preferred.

### LABORATORY SALIENT FINDINGS

- *Elevated urinary catecholamine:* HVA, VMA
- Plain X-ray, CT scan of primary tumor
- *Bone scan:* Periosteal lytic lesion of the skull
- Histopathological examination

## DIAGNOSTIC CRITERIA

The gold standard for the diagnosis of neuroblastoma is examination of tumor tissue by histopathology and immunohistochemistry. The criterias are:

- An unequivocal pathological diagnosis is made from tumor tissue by light microscopy, with or without immunohistochemistry, electron microscopy and/or increased urine catecholamines or metabolites ( $>3$  SD above the mean for age)

Or

- Bone marrow aspirate or biopsy containing unequivocal tumor cells, and increased urine catecholamines or metabolites ( $>3$  SD above the mean for age).

Other investigations include blood counts, urinary catecholamine excretion, bone marrow aspiration and biopsy, liver function tests, abdominal ultrasound, and X-ray and bone scan for metastasis. Nuclear scanning with I-123 or I-131 MIBG detects tumors and metastasis accurately. CT scans of chest, abdomen, and pelvis are indicated to assess extent of disease. MRI is preferred for paraspinal tumors to assess spinal cord compression.

## STAGING OF NEUROBLASTOMA

Clinical staging as per Evans (CCSG) staging system is done if surgery is not done upfront. International Neuroblastoma Staging System (INSS) is used

when surgical details are available and is one of the most important prognostic factors.

INSS	EVANS
<i>Stage 1</i> Localized tumor confined to the area of origin; complete gross excision with or without microscopic residual disease; identifiable ipsilateral and contralateral lymph nodes negative microscopically	<i>Stage I</i> Tumor limited organ or structure of origin
<i>Stage 2A</i> Unilateral tumor with incomplete gross excision; identifiable ipsilateral and contralateral lymph nodes negative microscopically	<i>Stage II</i> Tumor with regional spread that does not cross the midline; ipsilateral lymph node may be involved
<i>Stage 2B</i> Unilateral tumor with complete or incomplete gross excision; with positive ipsilateral lymph nodes, identifiable contralateral negative microscopically	
<i>Stage 3</i> Tumor with spread to midline with or without the involvement of regional lymph node or unilateral tumor with contralateral regional lymph node involvement or midline tumor with bilateral regional lymph node involvement	<i>Stage III</i> Regional tumor crossing the midline; bilateral lymph nodes may be involved
<i>Stage 4</i> Dissemination of tumor to distant lymph nodes, bone, bone marrow, liver and/or other organs	<i>Stage IV</i> Tumor with metastases to distant sites
<i>Stage 4-S</i> Localized primary tumor as defined for stage I or II with dissemination limited to liver, skin and/or bone marrow	<i>Stage IV-S</i> Localized primary tumor and disseminated disease limited to liver, skin and/or bone marrow

RISK STRATIFICATION

Risk stratification depends upon many factors which are as follows:

- Age
- Stage
- Pathology (Prechemotherapy biopsy or specimen)—the Shimada classification appears to have prognostic significance. It is based on histological features such as presence or

absence of stroma, degree of differentiation and mitosis-karyorrhexis index.

- *Biological factors:* Chromosome 1p deletion, DNA index

DIFFERENTIAL DIAGNOSIS

- Multicystic kidney
- Wilms’ tumor
- Pheochromocytoma
- Lymphosarcoma
- Hydronephrosis
- Brucellosis
- Teratoma

TREATMENT (TABLE 1)

The mainstay of therapy is surgical resection coupled with chemotherapy. Massive size of the tumor often makes primary resection impossible. Under these circumstances, only biopsy is performed. Following the chemotherapy, a surgical correction may allow the resection of primary tumor. Radiation therapy is also sometimes necessary.

Treatment depends upon the staging and severity.

Stages	International Neuroblastoma Staging System (INSS)
Stage I	: Confined to the area of origin with complete gross excision
Stage IIA	: Unilateral tumor with incomplete gross excision
Stage IIB	: Unilateral tumor with positive ipsilateral regional lymph nodes
Stage III	: Tumor infiltrating across the midline with or without regional lymph nodes
Stage IV	: Dissemination of tumor to distant lymph nodes, bone, bone marrow, liver, or other organs
Stage IV-S	: Localized primary tumor as defined with dissemination limited to liver, skin or bone marrow

*Stage I:* Surgery alone

*Stage IIA or 3 (<12 months):* Surgery followed by cyclophosphamide and adriamycin for 5 cycles.

*Stage IIB (>12 months):* Cyclophosphamide and adriamycin for five cycles with radiation therapy beginning at 3 weeks. If complete response obtained, patients should be treated with two more cycles of chemotherapy followed by two cycles of VM-26 and cisplatinum.

*Stage III (>12 months):* Surgical removal of primary tumor plus alternate cycles of chemotherapy with



**TABLE 1:** Treatment strategy based on risk categories of the patients.

<i>Risk</i>	<i>Stage</i>	<i>Age (year)</i>	<i>Treatment</i>	<i>Survival</i>
Low	1	Any	Surgery	90%
	2A/2B	Any	Surgery followed by low dose chemotherapy (cyclophosphamide and doxorubicin)	85–90%
	4S	<1	Observation if asymptomatic, chemotherapy/RT if symptomatic	
Intermediate	3	Any	Multiagent chemotherapy (cyclophosphamide, cisplatin, etoposide, doxorubicin) + 2nd look surgery ± RT to tumor bed ± lymph node ± maintenance chemotherapy	75%
	4	<1		
	4S	<1		
High	2A/2B	>1	Multiagent chemotherapy as induction, additional treatment such as MIBG therapy, high dose chemotherapy with autologous BMT as consolidation and biological therapy (13-cis-retinoic acid) as treatment of minimal residual disease	40–50%
	3	Any		
	4 and 4S	>1		
	4	>1		

OPEC and OJEC (OPEC: oncovin, cyclophosphamide etoposide and cisplatin; OJEC: oncovin, cyclophosphamide, etoposide and carboplatin).

*Stage IV (<12 months):* Initial surgery followed by 9–12 months of chemotherapy. (CADO: vincristine, cyclophosphamide, doxorubicin; PECADO: vincristine, cyclophosphamide, doxorubicin, cisplatin, and tenoposide)

Treatment strategies vary according to the risk groups. For identical age, stage and presence of unfavorable histology upgrades the patient to the next risk category.

The patients' age and tumor stage are combined with cytogenetic and molecular features of the tumor to determine the treatment risk group and estimated prognosis for each patient.

The usual treatment for children with low-risk neuroblastoma is surgery for stages 1 and 2 and observation for stage 4S with cure rates generally >90% without further therapy. Treatment with chemotherapy or radiation for the rare child with local recurrence can still be curative. Children with spinal cord compression at diagnosis also may require urgent treatment with chemotherapy, surgery, or radiation to avoid neurologic damage. Stage 4S neuroblastomas have a very favorable prognosis, and many regress spontaneously without therapy.

Chemotherapy or resection of the primary tumor does not improve survival rates, but for infants with massive liver involvement and respiratory compromise, small doses of cyclophosphamide or low-dose hepatic irradiation may alleviate symptoms. For children with stage 4S neuroblastoma who require treatment for symptoms, the survival rate is 81%.

Treatment of intermediate-risk neuroblastoma includes surgery, chemotherapy, and, in some

cases, radiation therapy. The chemotherapy usually includes moderate doses of cisplatin or carboplatin, cyclophosphamide, etoposide, and doxorubicin given for several months. Radiation therapy is used for tumors with incomplete response to chemotherapy. Children with intermediate-risk neuroblastoma, including children with stage 3 disease and infants with stage 4 disease and favorable characteristics, have an excellent prognosis and >90% survival with this moderate treatment.

Children with high-risk neuroblastoma have long-term survival rates between 25 and 35% with current treatment that consists of intensive chemotherapy, high-dose chemotherapy with autologous stem cell rescue, surgery, radiation, and 13-cis-retinoic acid (isotretinoin). Induction chemotherapy for children with high-risk neuroblastoma includes combinations of cyclophosphamide, topotecan, doxorubicin, vincristine, cisplatin, and etoposide. After completion of induction chemotherapy, resection of the residual primary tumor is followed by high-dose chemotherapy with autologous stem cell rescue and focal radiation therapy to tumor sites.

The further addition of 13-cis-retinoic acid after autologous stem cell transplantation resulted in further improvements in survival rates. In addition, a national clinical trial has demonstrated an increase in short-term survival rates with the addition of the monoclonal antibody ch14.18, interleukin 2, and granulocyte-macrophage stimulating factor to 13-cis-retinoic acid therapy.

Cases of high-risk neuroblastoma are associated with frequent relapses, and children with recurrent neuroblastoma have a <50% response rate to alternative chemotherapy regimens. New treatment strategies and agents are needed for

children with both high-risk and recurrent neuroblastoma. Therapies currently under investigation include new chemotherapeutic agents and other novel therapies directed against critical intracellular signaling pathways, radiolabeled targeted agents (such as  $^{131}\text{I}$ -MIBG), immunotherapy, and antitumor vaccines.

## RADIOTHERAPY

### Indications

- *Low-risk patients:* For symptomatic life or organ-threatening tumor
- *Intermediate-risk patients:* Whose tumor has responded incompletely to both chemotherapy and attempted resection and also has unfavorable biologic characteristics
- *High-risk patients:* Even in cases of complete resection
- *Bone marrow transplant:* As a part of preparatory regimen
- *Metastatic disease:* Palliative radiation therapy

## CONCLUSION

Neuroblastoma represents one of the most challenging malignancies for treatment decisions because of its unusual biological behavior which includes spontaneous regression at one end to

maturation to ganglioneuroma and treatment-resistant progression at other end of spectrum. The main achievements in the management of neuroblastoma during last two decades have been the reduction of chemotherapy in patients with low-risk disease and the increased efficacy of chemotherapy in high-risk disease.

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## PRESENTING COMPLAINTS

A 10-year-old boy was brought with the complaints of:

- Pain in the leg since 15 days
- Decreased movements since 15 days
- Swelling in the leg since 5 days

## History of Presenting Complaints

A 10-year-old boy came to pediatric outpatient department with history of pain in lower end of thigh. Mother complains that his son was apparently normal 15 days back. To begin with he developed pain in lower part of thigh and was shown to general practitioner. He was diagnosed to have myalgia and analgesics were given. Pain used to come down for time. After about a week pain in the thigh limited his movements. Child started to limp. His mother had noticed a small swelling at the site of pain. She then noted the swelling was

tender and hard then brought to the hospital for the specialist consultancy.

## Past History of the Patient

He was the second sibling of nonconsanguineous marriage. He was born at full term by normal vaginal delivery. There was no significant postnatal event. All the developmental milestones were normal. He had been completely immunized. His performance at school was satisfactory. He was a good athlete. He used to have minor usual ailments and for those he was getting the treatment by general practitioner. His elder sister maintained apparently good health.

## EXAMINATION

On examination, the boy was moderately built and nourished. He looked very much sick because of the pain. He came to the outpatient department by limping.

Anthropometric measurements included, height was 130 cm (25th centile) and the weight was 27 kg (50th centile). He was febrile, i.e., 38°C. The heart rate was 106 per minute and the respiratory rate was 24 per minute. The blood pressure recorded was 90/70 mm Hg.

Pallor was present. Localized edema was present at the lower end of the femur. There was inguinal lymphadenitis on the right side.

Local examination showed that there was palpable mass at the lower end of the femur. There was limitation of the movement and limping. There was tenderness and local erythema.

## INVESTIGATION

Hemoglobin	: 9 g/dL
TLC	: 7,600 cells/cu mm
DLC	: P <sub>80</sub> L <sub>18</sub> E <sub>2</sub>
Serum alkaline phosphatase	: 200 U/L (Normal range: 30–120 U/L)
Chest X-ray	: NAD

### CASE AT A GLANCE

#### Basic Findings

Height	: 130 cm (25th centile)
Weight	: 27 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 106 per minute
Respiratory rate	: 24 per minute
Blood pressure	: 90/70 mm Hg

#### Positive Findings

##### History

- Pain
- Limping
- Swelling

##### Examination

- Swelling
- Limping
- Tenderness
- Erythema

##### Investigation

- Alkaline phosphatase: Increased
- X-ray of femur: Sclerosis
- FNAC: Showed highly malignant pleomorphic spindle cells

X-ray of the femur	: Sclerosis, periosteal new bone formation. Showed well-defined soft tissue mass, sclerosis and lysis in medullary cavity
FNAC	: Malignant, pleomorphic spindle cells

## DISCUSSION

It is the most common malignant tumor of bone constituting nearly 20% of the malignant tumors of the bone. It occurs in the young between the ages of 10 and 20 years. It is more common in males. The common sites of occurrence are the distal end of femur (40%), the proximal end of tibia and the proximal end of humerus in the metaphysis.

The peak incidence occurs in the second decade of life when the most longitudinal growth occurs. The adolescent peak occurs at age 13 years in girls and between ages 15 and 17 years in boys, corresponding with the age of greatest growth velocity in each gender. The peak occurrence during the adolescent growth spurt suggests a casual relationship between rapid bone growth and malignant transformation.

Osteosarcoma is slightly more common in males. Other evidence supporting the relationship with growth includes its skeletal distribution with the majority occurring in regions that undergo the most extensive longitudinal growth. In addition, osteosarcoma typically occurs in the metaphyses of bones which is the site where new bone arises from the growth plates. Osteosarcoma is rare in children under age 5 years.

One well-known etiologic factor is ionizing radiation, although there is typically a long interval between irradiation and the development of osteosarcoma, making it less relevant to most pediatric patients. However, it should be noted that the incidence of osteosarcoma is markedly increased among survivors of hereditary retinoblastoma, who harbor germline mutations of the retinoblastoma gene. This risk is further increased in those who received radiotherapy as a component of their treatment. Similarly, germline mutations in the *p53* gene (the basis of Li-Fraumeni syndrome) can lead to a high risk of developing multiple malignancies including osteosarcoma.

Osteosarcoma is primary malignant tumor of the bone. It arises from the multipotent mesenchymal tissue of bone. Neoplastic cells will produce osteoid. They arise within medullary canal of shaft and may break through cortex of the bone of origin.

This will form shaft tissue mass. This can attain a considerable size. The tumor may extend along the medullary cavity.

There are some predisposing diseases to osteosarcoma. These include osteochondromatosis, multiple hereditary exostosis, osteogenesis imperfecta, and Paget's disease.

Radiation exposure is well-documented casual factor. It is known to occur in long time survivor of cancer who is treated with radiation therapy. It is highly malignant spindle cell neoplasm producing osteosarcoma.

## PATHOLOGY

The tumor is located in the metaphyseal region and reaches the subperiosteal area through the cortex. It is grayish white, the consistency may be hard and fleshy with streaks of tumor bone or it may be soft and vascular with areas of hemorrhage. The tumor edge stops at the epiphyseal cartilage and does not break through it. The tumor also extends into the medullary canal. In advanced cases, the tumor breaks through the periosteum, invades the soft tissues and even fungates through the skin.

The most characteristic features are the anaplastic sarcomatous stroma with newly formed woven bone and the presence of malignant osteoid. It may also show areas of malignant cartilage and fibrous tissue. The stromal cells are spindle shaped osteoblasts showing excessive mitosis, pleomorphism and hyperchromatism. There may be areas of hemorrhage and necrosis.

## PATHOGENESIS

Although the cause of osteosarcoma is unknown, certain genetic or acquired conditions predispose patients to development of osteosarcoma. Patients with hereditary retinoblastoma have a significantly increased risk for development of osteosarcoma. Predisposition to development of osteosarcoma in these patients may be related to loss of heterozygosity (LOH) of the *RB* gene. Osteosarcoma also occurs in the Li-Fraumeni syndrome, which is a familial cancer syndrome associated with germline mutations of the *P53* gene.

The pathologic diagnosis of osteosarcoma is made by demonstration of a highly malignant, pleomorphic, spindle cell neoplasm associated with the formation of malignant osteoid and bone. There are four pathologic subtypes of conventional high-grade osteosarcoma—osteoblastic, fibroblastic, chondroblastic, and telangiectatic.

Osteosarcoma has some important classification as follows:

- *Parosteal osteogenic sarcoma* (also called juxtacortical osteosarcoma) is well-differentiated extramedullary tumor. This has got a low metastatic potential. This tumor is found exclusively in long bones, e.g., femur and shows extensive central ossification. Parosteal osteosarcoma is low grade, well-differentiated tumor that does not invade the medullary cavity and most commonly is found in the posterior aspect of the distal femur. Surgical resection alone often is curative in this lesion, which has a low propensity for metastatic spread.
- *Periosteal osteogenic sarcoma*: It is histologically pleomorphic lesion. It clinically behaves more aggressively. Periosteal osteosarcoma is a rare variant that arises on the surface of the bone but has a higher rate of metastatic spread than the parosteal type and an intermediate prognosis.
- *Telangiectatic osteosarcoma* is a bloody cystic lesion. It is confused with aneurysmal bone cyst.

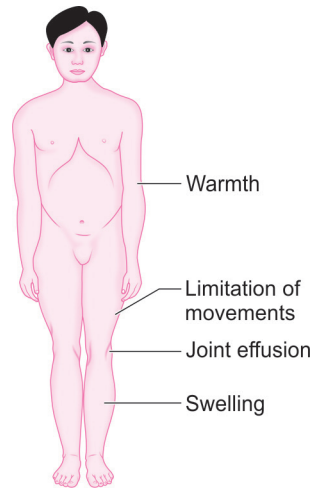
## CLASSIFICATION

Osteosarcomas are broadly classified as:

- *Central (intramedullary) type*:
  - Primary
    - ♦ Conventional
    - ♦ Telangiectatic
    - ♦ Small cell
    - ♦ Multicentric
  - Secondary
    - ♦ Paget's disease
    - ♦ Radiation induced
    - ♦ Arising from other benign conditions such as fibrous dysplasia and osteochondroma
- *Juxtacortical (surface) type*:
  - Parosteal
  - Periosteal
  - Differentiated

## CLINICAL FEATURES (FIG. 1)

The onset of the disease is more common among the adolescent period. The mean age of the onset is 15 years. It occurs more frequently within long bones at metaphyseal ends. These are places of most active growth and reconstruction. The most common primary site is distal femur, proximal humerus and proximal tibia. The children with bilateral retinoblastoma have increased incidence



**Fig. 1:** Clinical features.

of osteosarcoma. The gene associated with retinoblastoma may predispose the patient to osteosarcoma as well.

The highest risk period for development of osteosarcoma is during the adolescent growth spurt, suggesting an association between rapid bone growth and malignant transformation. Patients with osteosarcoma are taller than their peers of similar age.

The most common initial finding is pain at the site of the tumor. Later there is limitation of movements. Palpable or visible tumor may develop. There may be limping or alteration in gait with involvement of legs and pelvis. There will be tenderness and local erythema, and hyperthermia may occur.

On examination, the swelling is fusiform; the skin is stretched, shiny and vascular with prominent veins. The swelling is warm to touch and may also show pulsation if the tumor is very vascular. It is firm to hard in consistency with areas of softening where the tumor has invaded the soft tissues. In the later stages, the tumor fungates. The patient's general health deteriorates with anemia, loss of weight and cachexia. The patient develops pulmonary symptoms due to secondaries in lungs.

### ESSENTIAL DIAGNOSTIC POINTS

- Long tubular bones, arises from metaphysis
- Pain is the initial symptom
- Bone swelling, progressively increasing in size
- Radiography; trabecular pattern with indistinct margin
- Limping and limitation of movements
- Pleural effusion and pneumothorax

The common site of metastasis is lung. Pleural effusion and pneumothorax can occur. Other sites



of metastasis include other bones, hilar lymph node, and central nervous system.

#### GENERAL FEATURES

- Pain
- Tenderness
- Fever

### DIAGNOSIS

Persistent unexplained bone pain, associated with palpable mass, requires radiography. In radiograph sclerosis of the bone and periosteal new bone formation are common. It shows permeative destruction of normal bony trabecular pattern with indistinct margin.

The tumor arises at the metaphyseal region of the bone, either centrally or over the cortex. There are mottled areas of rarefaction with areas of osteosclerosis. When it extends beyond the cortex, the periosteum is raised and there is new bone formation in lines at right angles to the cortex. This causes the “sun ray” appearance on the radiograph. There is also reactive new bone formation subperiosteally to the junction of the lifted periosteum and the normal bone. This is called Codman’s triangle. The radiographs may also show a pathological fracture.

Radiograph of the chest must be taken. It may show round shadows caused by secondary deposits (“cannon ball” appearance).

Results or routines laboratory tests, such as a complete blood cell count and chemistry panel, are usually normal, although alkaline phosphatase or lactate dehydrogenase values may be elevated. The recommended imaging studies for osteosarcoma at the time of diagnosis are a plain radiograph and magnetic resonance imaging (MRI). As with other musculoskeletal conditions, such as slipped capital femoral epiphysis (SCFE), symptom localization in osteosarcoma may not be precise. Consequently, if symptoms persist and imaging is negative, obtaining imaging of adjacent bones or joints should be considered.

A plain radiograph is often the most appropriate initial test to order if the presence of a malignant bone tumor is suspected. A plain radiograph often identifies the anatomic region of abnormality and shows features of the bone and tumor that help narrow the differential diagnosis. On plain radiographs, osteosarcoma usually has a mixed pattern of bone lysis and sclerosis, the boundary between tumor and normal bone is usually irregular, and the bone cortex is often disrupted by tumor growth into the surrounding soft tissue. Osteoid formation within the tumor results in areas

of calcification visible in the bony and soft tissue components of the tumor. Periosteal new bone formation in osteosarcoma can be irregular or can occur in a sunburst pattern. MRIs should be performed with contrast, and the entire bone from which the tumor arises as well as the closest adjacent joint should be imaged.

Before biopsy, MRI of the primary lesion and the entire bone should be performed to evaluate the tumor for its proximity to nerves and blood vessels, soft tissue and joint extension, and skip lesions. The metastatic workup, which should be performed before biopsy, includes CT of the chest and radionuclide bone scanning to evaluate for lung and bone metastases, respectively.

The tumor is pleomorphic, spindle cell tumor that forms an extracellular matrix of osteoid. Metastatic bony lesion and lung involvement must be looked at. It includes CT scan of the chest. MRI provides the best assessment of tumor extent to plan surgery.

In all cases, the diagnosis should be established by a biopsy. This should be done at the growing periphery of the tumor, which gives the typical microscopic appearance. Positron emission tomography-computed tomography (PET-CT) may be considered in monitoring the response to treatment.

#### LABORATORY SALIENT FINDINGS

- *Radiographic findings:* Mottled areas of rarefaction, periosteum is raised, new bone formation in lines at right angles to cortex (sun ray appearance)
- CT scan and MRI of chest and bone scan
- Biopsy
- Histopathological examination

### DIFFERENTIAL DIAGNOSIS

- Ewing’s sarcoma
- Osteomyelitis
- Septic arthritis

### TREATMENT

Broadly speaking the treatment of osteosarcoma is usually a combination of surgery, radiotherapy and chemotherapy. Osteosarcomas are fully radio-resistant lesion.

**Surgery:** Complete surgical resection of the tumor is important for cure. The current approach is to treat patients with preoperative chemotherapy in an attempt to facilitate limb salvage operations and to treat micrometastatic disease immediately. Up to 80% of patients are able to undergo limb salvage operations after initial chemotherapy. It is important to resume chemotherapy as soon as

possible after surgery. Lung metastases present at diagnosis should be resected by thoracotomies at some time during the course of treatment. Active agents currently in use multidrug chemotherapy regimens for conventional osteosarcoma include doxorubicin, cisplatin, methotrexate, and ifosfamide.

A limb saving surgery may be possible if the case is diagnosed early and the lesion is small. In such a situation, after neoadjuvant chemotherapy, the lesion is excised widely, including a margin of normal tissue all around and the gap thus created may be bridged by bone grafts or artificial prosthesis whatever is feasible.

Amputation remains the main stay of treatment if limb salvage is not feasible. The amputation can be a palliative amputation if the disease is advanced. In this situation, the goal of operation is either pain relief or to prevent complications in a fungating tumor. A definitive amputation removes the tumor completely. The level of amputation and the length of the remaining stump of the limb, etc., can be better planned.

For patients who require amputation, early prosthetic fitting and gait training are essential to enable patients to resume normal activities as soon as possible. Before definitive surgery, patients with tumors of weight-bearing bones should be instructed to use crutches to avoid stressing the weakened bones and causing pathologic fracture. The role of chemotherapy in parosteal and periosteal osteosarcomas is not well defined, and chemotherapy is generally reserved for use in patients with tumors which have a high-grade microscopic appearance.

Contraindications for limb-sparing surgery include major involvement of the neurovascular bundle by tumor, immature skeletal age, inappropriate biopsy site, and extensive muscle involvement.

**Radiotherapy:** It is indicated for local control of the disease after incomplete surgical removal of the tumor and also for tumors situated at surgically inaccessible sites.

**Chemotherapy:** It is often administered prior to the definitive surgery—neoadjuvant therapy. This permits an early attack on micrometastatic disease and may also shrink the tumor, facilitating limb salvage procedure. Preoperative chemotherapy makes detailed histologic evaluation of tumor response to chemotherapy agents possible. If the histological response is poor postoperative chemotherapy can be changed accordingly. Chemotherapy can be given intra-arterially or intravenously.

It consists of drugs, methotrexate, bleomycin, cyclophosphamide, adriamycin, doxorubicin, ifosfamide, and cisplatin, given pre- and/or postoperatively to control the micrometastasis. A regular follow-up every 3 months is mandatory to detect any recurrence or spread of the tumor in time. Postsurgical chemotherapy is generally continued until patient received 1 year of treatment.

## PROGNOSIS

Prognosis is best with low-grade tumor such as parosteal osteosarcoma, or juxtacortical osteosarcoma. More than two-thirds of the patients presenting without metastasis have long-term survival and are cured. The cure rate in metastasis disease is less than 25%.

One of the most important prognostic factors in osteosarcoma is the histologic response to chemotherapy. An international cooperative group is performing a randomized trial of the post-operative addition of high-dose ifosfamide with etoposide to standard three-drug therapy with cisplatin, doxorubicin, and methotrexate to improve the income patients with a poor histologic response. After limb salvage surgery, intensive rehabilitation and physical therapy are necessary to ensure maximal functional outcome.

The most important prognostic factor in the treatment of osteosarcoma is the presence of grossly visible metastatic disease at the time of diagnosis, which confers a much worse prognosis. That general principles of treatment for these patients remain the same, including chemotherapy and resection of all sites of bulk disease, including pulmonary metastases. Other adverse prognostic factors include older age and an unresectable primary tumor, which can be related to tumor site or tumor size. Approximately 80% of patients with osteosarcoma are diagnosed with localized disease, and with current therapy 60–70% of those patients will be long-term survivors.

Patients with localized disease having 90% or greater tumor necrosis have 70–75% long-term disease for survival rate. Favorable prognostic factors include distal skeletal lesion, longer duration of symptoms age, older than 20 years, female gender, near diploid tumor, and DNA index.

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# Retinoblastoma

## PRESENTING COMPLAINTS

A 20-month-old boy was brought with the complaints of:

- Asymmetric movements of eyeball since 2 months
- Doubtful vision in the left eye since 1 month

## History of Presenting Complaints

A 20-month-old boy was brought to the pediatric outpatient department with history of squint in left eye. His mother complained that her son was apparently normal till 2 months back. Later she noticed the asymmetric movement of the eyeball. It was more on the left side. She even developed the doubt that whether the child could see with left eye. Hence, she brought him to the hospital. There was no history of pain or trauma to eye.

## Past History of the Patient

The boy was the only sibling of consanguineous marriage. He was born at full term by normal vaginal delivery. The baby cried immediately after the delivery. There was no significant postnatal

event. Mother and child were discharged on third day. The child was on breast milk exclusively for the first 3 months. Weaning started later, and child was on normal family food from 15 months. All the developmental milestones are normal. He had been completely immunized.

## EXAMINATION

Child was moderately built and nourished. He was playing with toys on examination table. On careful observation, it was found that he was moving his whole body for toys on left side to play with them.

There was conjugate gaze on left eye. Eye examination revealed presence of loss of vision on left eye with squint. Anthropometric measurements included, the height was 83 cm (50th centile), the weight was 11 kg (75th centile). The head circumference was 46 cm.

He was febrile, the heart rate was 116 per minute, the respiratory rate was 26 per minute. The blood pressure recorded was 60/46 mm Hg. There was no pallor, no lymphadenopathy. There was no cyanosis and clubbing. Fundus examination showed presence of white reflex. Other systemic examinations were normal.

## CASE AT A GLANCE

### Basic Findings

Height	: 83 cm (50th centile)
Weight	: 11 kg (75th centile)
Temperature	: 38°C
Pulse rate	: 116 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 60/46 mm Hg

### Positive Findings

#### History

- Squint
- Doubtful of vision

#### Examination

- Loss of vision
- Squint

#### Investigation

- *Fundoscopy*: Presence of white reflex
- *Plain X-ray skull*: Calcification

## INVESTIGATION

Hemoglobin	: 13 g/dL
TLC	: 7,600 cells/cu mm
ESR	: 32 mm in the 1st hour
AEC	: 340 cells/dL
Plain X-ray skull	: Calcification is seen within the globe
Fundoscopy	: Presence of white reflex is evident

## DISCUSSION

Retinoblastoma is the most common primary malignant intraocular tumor of childhood. It occurs in approximately 1 in 20000 infants.

Retinoblastoma is an embryonal malignancy of the retina and the most common intraocular

tumor in children. Retinoblastoma progresses to metastatic disease and death in over 50% of children worldwide.

In heritable cases, the first mutation arises during gametogenesis, either spontaneously (90%), or through transmission from parents (10%). This mutation is present in every retinal cell and in all other somatic and germ cells. Ninety percent of persons who carry this germ line mutation will develop retinoblastoma.

For tumor formation, loss of second retinoblastoma (*RB1*) gene allele within the cell must occur. Loss only is insufficient for tumor formation. The second mutation occurs in somatic (retinal) cell.

Inheritable cases (60%) both mutation arise in somatic cell after gametogenesis has taken place.

Hereditary and nonhereditary patterns of transmission occur; there is no sex or race predilection. The average age at diagnosis for bilateral tumors is 12 months and for unilateral tumors it is 21 months.

In trilateral retinoblastoma syndrome, pineal tumors develop in approximately 1 in 100 patients with bilateral ocular disease. Characteristically, the diagnosis is made by ophthalmoscopic, radiographic and ultrasonographic appearance, without pathologic confirmation. The locus is present on chromosome no. 13. It is associated with osteosarcoma, pineal tumor, lung and breast cancer.

## Genetics and Molecular Biology

It occurs either spontaneously or as an inherited disorder. Retinoblastoma shows an autosomal dominant inheritance pattern with high penetrance. Approximately 55% of tumor occur as nonhereditary, unifocal, unilateral tumor.

An additional 15% are unilateral, but are hereditary with a family history. Thirty percent occur as heritable bilateral unifocal or multifocal tumors. Hereditary cases usually are diagnosed at a younger age and are multifocal and bilateral, whereas sporadic cases are usually diagnosed in older children who tend to have unilateral, unifocal involvement.

The *RB1* gene is a tumor suppressor gene and retinoblastoma tumors are homozygous for chromosome 13q14 abnormalities with either deletions or alterations of genetic material at that locus. The hereditary form is associated with loss of function of the *RB1* gene via gene mutation or deletion. The *RB1* gene is located on chromosome 13q14 and encodes the retinoblastoma protein, a tumor-suppressor protein that controls cell-cycle

phase transition and has roles in apoptosis and cell differentiation. Hereditary cases show a germ-line abnormality in one gene at this locus. Some affected children have other systemic features of the 13q deletion syndrome.

Genetic counseling for patients with retinoblastoma and their families is complex, but a few generalizations can be made. Patients with the hereditary form are at risk for other cancers later in life, including soft tissue and bone sarcomas and melanoma. This risk is increased in patients treated with radiotherapy. It is estimated that 10% of individuals who carry an abnormal *RB1* gene do not develop retinoblastoma because the second event did not occur in any cell; however, they are still at risk of developing other cancers during their lifetime.

## **PATHOLOGY**

This tumor which usually arises from the posterior portion of the retina, consists of small round closely packed malignant cells with scanty cytoplasm. Tumor may grossly appear crumbly and friable with gelatinous areas of degradation, patches of calcification or pigmented hemorrhage. It may appear as a single tumor in the retina, but typically has multiple foci.

Tumors can also be both endophytic and exophytic. The growth may be endophytic (forward into the vitreous cavity) or exophytic (into the subretinal space with detachment of retina). Endophytic tumors arise from the inner surface of the retina and grow into the vitreous, and can also grow as tumors suspended within the vitreous itself, known as vitreous seeding. Exophytic tumors grow from the outer retinal layer and can cause retinal detachment. Diffuse infiltrating tumors grow intraretinally and remain flat. These are less common and can cause iris neovascularization. The tumor fragments may break off and float free in the vitreous to seed other parts of retina. The most frequent extraocular sites of involvement are the optic nerve, orbit and periorbital tissues, cranial tissue, bone and bone marrow.

Histologically, retinoblastoma appears as a small round blue cell tumor with rosette formation (Flexner-Wintersteiner rosettes). It may arise in any of the nucleated layers of the retina and exhibit various degrees of differentiation. Retinoblastoma tumors tend to outgrow their blood supply, resulting in necrosis and calcification.

These tumors can also spread by direct extension to the choroid or along the optic nerve beyond the lamina cribrosa to the central nervous

system, or by hematogenous or lymphatic spread to distant sites, including bones, bone marrow, and lungs.

**CLINICAL FEATURES (FIG. 1)**

It is the most common primary ocular tumor of childhood arising from embryonic retina. This occurs between 3 and 5 years. There is no sex predilection.

The most common presenting sign of retinoblastoma is leukocoria. When a tumor is small and at the macula, the initial sign may be sensory strabismus. When disease is very advanced, presenting symptoms may include pain due to secondary glaucoma, buphthalmos, proptosis, hyphema, or orbital cellulitis.

The differential diagnosis of retinoblastoma includes persistent hyperplastic primary vitreous (PHPV), retinal detachment, Coats disease, glial hamartoma, retinal hemangioma, myelinated nerve

fibers, congenital cataract, chorioretinal coloboma, uveitis, larval granulomatosis, congenital retinal folds, retinal dysplasia, and retinopathy of prematurity.

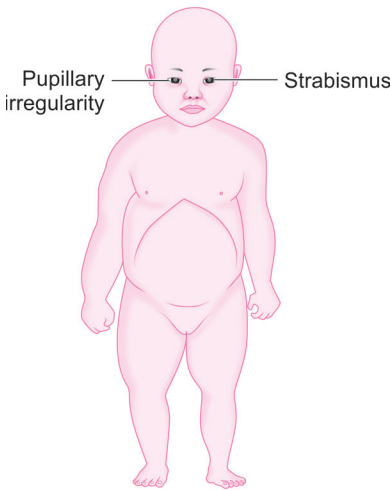
The tumor usually presents with leukocoria, i.e., yellow white reflex in the pupil (**Figs. 2A and B**). Other presenting complaints may be loss of vision reflected as a squint in the affected eye. The other symptoms may be pain, pupillary irregularity and hyphema. Proptosis may present with advanced tumor. There may be signs of increased intracranial pressure. There may be bone pain associated with metastatic disease.

The common presenting sign is strabismus followed by painful glaucoma, redness of eye, diminished vision.

Tumor spreads locally-bones, cerebrospinal fluid (CSF), bone marrow, liver and spleen. Extension of retinoblastoma into choroid usually occurs with massive tumors. This may indicate hematogenous metastasis. Extensions of tumor through lamina cribrosa and optic nerve will lead to involvement of central nervous system.

For proper staging, children should have computed tomography (CT) scan of the orbit and skull assessment of local orbital and intracranial extension, bone marrow biopsy and CSF examination for cytology.

Rarely, a painful eye with glaucoma, a hyphema or proptosis are the initial manifestation. Bilateral involvement is seen in 20–30% of children.



**Fig. 1:** Clinical features.

**GENERAL FEATURES**

- White pupillary reflex
- Orbital inflammation
- Hyphemia
- Glaucoma
- Retinal detachment



**Figs. 2A and B:** Leukocoria.  
(For color version see Plate 8)



**ESSENTIAL DIAGNOSTIC POINTS**

- It is the neuroectodermal malignancy
- Arises from embryonic retinal cells
- Leukocoria, unusual appearance asymmetry of eyes
- Strabismus is present

**DIAGNOSIS**

Diagnosis is by finding of the leukocoria. Other causes of white reflex include retinal detachment, hyperplasia of primary vitreous, visceral larva migrans, cataract, coloboma of choroid, and retinopathy of prematurity. The findings of leukocoria must be followed by careful fundoscopic examination under anesthesia.

Indirect ophthalmoscopy with slit-lamp evaluation can detect retinoblastoma tumors, but a complete evaluation requires an examination under general anesthesia by unexperienced ophthalmologist to obtain complete visualization of both eyes, which also facilitates photographing and mapping of the tumors. Retinal detachment or vitreous hemorrhage can complicate the evaluation.

Orbital ultrasonography, CT, or magnetic resonance image (MRI) is used to evaluate the extent of intraocular disease and extraocular spread. Occasionally (60%), a pineal area (primitive neuroectodermal) tumor is detected in a child rise in with hereditary and bilateral retinoblastoma, a phenomenon known as trilateral retinoblastoma. MRI allows for better evaluation of optic nerve involvement.

Computed tomography scan of the orbit should be performed to evaluate extent of tumor and to assess whether optic nerve, bony structures or pineal gland are involved. Most intraocular retinoblastoma shows evidence of intratumoral calcification.

Ultrasound may aid in the differential diagnosis, which include other causes of leukocoria such as retinal detachment or dysplasia, retinopathy of prematurity, persistent hyperplastic vitreous, nematode endophthalmitis, cataract, coloboma of the choroids. An ultrasound of the globe can demonstrate the presence of calcium, which is typical of retinoblastoma.

Magnetic resonance image of the brain is an essential part of the assessment of all children with hereditary retinoblastoma because of the association of a primitive neuroectodermal tumor in the brain, most commonly located in the pineal region. This trilateral retinoblastoma syndrome is usually diagnosed at a very young age, and

screening and early detection may improve survival. If metastatic disease is a consideration, an MRI of the brain and spine, bone scan, bone marrow aspiration and biopsy, and a lumbar puncture to examine the cerebrospinal fluid for tumor cells should be performed. These are not routinely indicated if the history, examination, blood count, and MRI indicate intraocular disease only.

Radionuclide bone scan and examination of bone marrow and CSF for tumor cells are necessary only if there is evidence of trans-scleral extension or extension beyond the cut end of optic nerve. Metastatic disease of the bone marrow and meninges can be ruled out with bilateral bone marrow aspiration and biopsies plus CSF cytology.

**LABORATORY SALIENT FINDINGS**

- *Fundus examination:* White or creamy pink mass protruding into the vitreous
- CT scan of the orbit
- Bone marrow aspirate and biopsy
- CSF cytology
- Bone scan, CT scan of liver

**DIFFERENTIAL DIAGNOSIS**

- Retinal detachment
- Vitreous hemorrhage
- Cataract
- Choroidal coloboma
- Retinopathy of prematurity

**TREATMENT**

The primary goal of treatment is always cure; the secondary goals include preserving vision and the eye itself and decreasing the risk of late side effects, mainly secondary malignancies.

The modalities of treatment include photocoagulation, localized radioactive plaque, and systemic chemotherapy.

Cryotherapy, photocoagulation and radioactive plaques can be used for local tumor control.

It is highly curable when the disease is intraocular. Local therapy includes cryotherapy, photo (laser) coagulation, brachytherapy (plaque) radiation and/or external beam radiotherapy. It enhances the risk of secondary malignancy.

Local ophthalmic measures include laser photocoagulation, thermotherapy, and/or cryotherapy.

Laser therapy includes Argon or diode laser is the primary treatment for smaller tumors, but is also sometimes used after chemoreduction.

*Cryotherapy:* A special probe is applied through the sclera to produce low temperature (−60 to −80°C)

is suitable for tumors smaller than 4 disc diameters close to retina.

**Chemotherapy:** It enables salvaging the affected eye, avoiding enucleation or external beam radiotherapy and risk of secondary malignancies. Systemic chemotherapy includes combination of vincristine, carboplatin and etoposide. Chemotherapy may also be used for chemoreduction, as an adjunct modality or for therapy of metastasis. Newer routes of drug (melphalan, carboplatin) administration by periocular, intravitreal and intraophthalmic artery injection have improved outcomes in intraocular retinoblastoma.

**Radiotherapy:** External beam radiotherapy is considered, if chemotherapy and focal therapy fail. Radiotherapy may lead to orbital deformity, sicca syndrome, cataract, radiation retinopathy, neovascular glaucoma and risk of a second malignancy.

**Hematopoietic stem cell transplantation:** Patients with extraocular disease have poor prognosis with respect to the survival. Those with regional extraocular disease (involving orbit, optic nerve or periauricular region) may be treated with a combination of conventional chemotherapy and external beam radiotherapy. Patients with distant metastasis require high dose chemotherapy, external beam radiotherapy and hematopoietic stem cell transplantation.

Photocoagulation is generally used for small tumors confined to the retina. Peripheral tumors too large to be treated effectively with photocoagulation may be treated more appropriately with cryotherapy. This combined approach of chemoreduction followed by local therapy has been shown to improve visual outcome and delay or avoid external beam radiation and enucleation. More recently, promising alternate routes of chemotherapy delivery such as intra-arterial (ophthalmic artery) or intravitreal injections have been employed in an attempt to preserve the affected eyes in both unilateral and bilateral retinoblastoma.

Most unilateral disease presents with a solitary, large tumor. Enucleation is performed if there is no potential for the salvage of useful vision. With bilateral disease, chemoreduction in combination with focal therapy (laser photocoagulation or cryotherapy) has replaced the traditional approach of enucleation of the more severely affected eye and irradiation of the remaining eye. The dose of the irradiation is 4000–4500 rads if there is painful

glaucoma eye should be enucleated. Irradiation is preferred if tumor is very small.

Absolute indications for enucleation are no vision, glaucoma, inability examine the treated eye, and inability to control tumor growth conservative treatment.

If feasible, small tumors can be treated with focal therapy with careful follow-up for recurrence or new tumor growth. Larger tumors often respond to multiagent, chemotherapy, including carboplatin, vincristine, and etoposide. If this approach fails, external-beam irradiation should be considered, although this approach may result in significant orbital deformity and increased incidence of second malignancies in patients with germ-line *RBI* mutations. Brachytherapy, or episcleral plaque radiotherapy, is an alternative with less morbidity. Enucleation may be required for unresponsive or recurrent tumors.

When enucleation is planned an attempt should be made to resect as much optic nerve as possible, i.e., 10 mm or more. Radiation therapy should be considered if there is regional extraocular extension of tumor has been found at the time of enucleation.

Chemotherapy is also used as an adjunct to primary surgery in those cases that are high risk for metastases, such as eyes with optic nerve, massive choroidal or scleral invasion. Children with metastatic retinoblastoma require more intensive therapy. Modalities include systemic chemotherapy, external beam radiotherapy, and high-dose chemotherapy followed by autologous hematopoietic stem cell rescue.

Patients with extraocular and metastatic disease or those considered to be a great risk for metastatic disease because of significant involvement of choroid, sclera or ciliary body or because of extension of tumor beyond lamina cribrosa should be treated with combination chemotherapy probably including carboplatin, etoposide and vincristine.

Local therapy such as laser therapy, cryotherapy, radiotherapy or enucleation should be considered depending upon the response to chemotherapy. Bone marrow transplantation has been advocated for metastatic retinoblastoma.

## PROGNOSIS

The overall survival rate is more than 90%, although survival into the third and fourth decades of life may be decreased considerably, by the high incidence of second malignancies. The prognosis is directly related to the size and extension of

the tumor. Most tumors that are confined to the eye can be cured. Cures are infrequent when extensive orbital or optic nerve extension has occurred or patient has CNS or distal metastasis.

Children with retinoblastoma confined to the retina (whether unilateral or bilateral) have excellent prognosis with 5-year survival rate more than 90%. Mortality is directly correlated directly with optic nerve involvement, orbital extension of tumor and choroid invasion. Patient's disease in optic nerve beyond the lamina cribrosa have 5-year survival rate of 40%. Meningeal and metastatic spread will rarely survive.

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## PRESENTING COMPLAINTS

A 6-year-old girl was brought with the complaints of:

- Abdominal pain since 3 days
- Fever since 2 days
- Breathlessness since 1 day

## History of Presenting Complaints

A 6-year-old girl presented with history of abdominal pain for 3 days. The pain was present in right side. There was radiation of pain down to medial aspects of thigh. Mother also gave history of fever which was moderate to high degree. It used to be intermittent and more so in evening. It was associated with chills and rigors. There was no history of vomiting and bowel disturbances. Later child becomes much toxic, restless and also breathless. Then the child was brought to the hospital.

### CASE AT A GLANCE

#### Basic Findings

Height	: 116 cm (75th centile)
Weight	: 15 kg (25th centile)
Temperature	: 38°C
Pulse rate	: 120 per minute
Respiratory rate	: 40 per minute
Blood pressure	: 90/60 mm Hg

#### Positive Findings

##### History

- Abdominal pain
- Fever

##### Examination

- Abdominal mass
- Tenderness
- Abdominal distension
- PSM of grade 3/6

##### Investigation

- *Urine*: RBCs ++, Protein ++
- *Ultrasound abdomen*: Large mass, displaced aorta, IVC not visible
- *Excretory urogram*: Displacement of pelvis and calyces

## Past History of the Patient

She was the second sibling of consanguineous marriage. She was delivered at term by normal vaginal delivery. She cried immediately after the delivery. There was no significant postnatal event. The child was on breast milk exclusively for the first 4 months. Later weaning was started, and child was on family food by 15 months of age. She never had any urinary and bowel disturbances. She had been completely immunized. Her developmental milestones were normal. Her performance at school was above average.

## EXAMINATION

The child was moderately built and nourished. She was looking much anxious. She was pale. Anthropometric measurements included, her height was 116 cm (75th centile), and weight was 15 kg (25th centile).

She was febrile, the pulse rate was 120 per minute, and the respiratory rate was 40 per minute. The blood pressure recorded was 90/60 mm Hg. There was pallor, no clubbing, no cyanosis and no lymphadenopathy.

Per abdomen examination revealed presence of abdominal distension. A large mass was palpable. It was present on right loin and was tender. Bowel sounds were normal. Cardiac examination revealed presence of grade 3/6 pansystolic murmur in left sternal edge.

## INVESTIGATION

Hemoglobin	: 6 g/dL
TLC	: 9,660 cells/cu mm
ESR	: 36 mm in 1st hour
Urine examination	: Protein ++ RBCs ++
Ultrasound abdomen	: Normal organs could not be visualized because of large right sided mass. Aorta is displaced to left kidney and IVC cannot be visualized

Excretory urogram : Showed tumor originating from lower pole of kidney displacing pelvis and calyces upwards

## DISCUSSION

Large right sided abdominal mass with hematuria suggests nephroblastoma. The child started developing signs of tricuspid regurgitation possibly because of disruption of tricuspid valve due to tumor thrombus impinging on valve. Congestive cardiac failure should be treated first.

Wilms' tumor (WT) develops as a result of abnormalities in the development of metanephric blastoma. It is the second most common malignant tumor of abdomen in childhood. It is the most common malignant tumor of kidney. Bilateral disease is more common among familial type.

It is congenital in origin. The usual age of onset is 4 months to 6 years. It is mainly unilateral. About 5–10% may have bilateral disease. 1.5% cases of Wilms' tumor are familial. It constitutes 6% of all childhood cancers.

Tumor appears as a large well-defined capsulated mass that replaces the kidney tissue. It is soft and pliable. It may grow into the surrounding tissues. Metastasis occurs in liver and lungs. Prognosis is better in tumors with the dominance of epithelial components.

## EPIDEMIOLOGY

The median age at diagnosis of WT is approximately 3.5 years, with some variation based on gender and ethnic group. The majority of WT cases occur prior to 5 years of age, and WT is very rare in children over 10 years of age. Renal cell carcinoma (RCC) is the second most common renal neoplasm in pediatric and adolescent patients, accounting for 2–6% of renal malignancies in this age group. While WT is more common in younger children, RCC is most common in ages 15–19 years old.

Wilms' tumor cases have been reported are WAGR (Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation), Denys-Drash (WT diffuse mesangial sclerosis leading to early-onset renal failure, and intersex disorders that can range from ambiguous to normal-appearing female genitalia in-both. XY and XX individuals), and Beckwith-Wiedemann (embryonal tumors, macrosomia, macroglossia, hemihyperplasia, visceromegaly; omphalocele, neonatal hypoglycemia, and ear creases/pits) syndromes.

Wilms' tumor has been reported to be associated with hemihypertrophy, aniridia, genitourinary anomalies and various anomalies. Genitourinary anomalies are the most common and account for incidence of 4–8%. The anomalies include fused kidney, renal dysplasia, cryptorchidism, hypospadias, duplication of the collecting system, WAGR syndrome. Wilms' tumor is also featured in many disorders of overgrowth including Beckwith-Wiedemann syndrome, Perlman syndrome and isolated hemihypertrophy.

Although most patients with WT are karyotypically normal, genomic studies have led to the localization and subsequent cloning of *WT* genes in two regions-11p13 and 11p15. The former is *WT1* gene and is associated with WAGR syndrome and the latter is *WT2* gene which is associated with Beckwith-Wiedemann syndrome.

The important deletion that is found in patients with WT is the deletion in the region of 11p13 with large deletion malformation such as mental retardation, aniridia, abnormal genitalia are found.

## PATHOLOGY

While the classic description of WT is of triphasic morphology, including blastemal, stromal, and epithelial elements, remarkable histologic diversity can be seen among these tumors. The variety of cellular types and patterns that are normally seen in the developing kidney can be found in WT. Further, tissues that are not usually noted within the kidney, such as skeletal muscle, cartilage, and squamous epithelium, also can be present. It is postulated that a variety of cell types arise due to the pluripotent potential of the primitive metanephric blastemal cells. On gross examination, areas of tumor within the kidney are well-circumscribed, lobular masses, and are usually gray or pink in color. Multiple nodules of differing size can be found, and cystic changes, necrosis, and, hemorrhage are often seen. These tumors are frequently friable.

The classic triphasic WT (favorable histology), is made up of varying proportions of three cells types—blastoma, stromal and epithelial cells, recapitulating stages of normal renal development. Unfavorable histology is characterized by qualitative variation from the classical type. Presence of focal or diffuse anaplasia, clear cell sarcoma and rhabdoid tumor are considered to be unfavorable histologic features. Most WTs are unicentric, 11% are multicentric but unilateral and 7% are bilateral.



**ESSENTIAL DIAGNOSTIC POINTS**

- Asymptomatic abdominal mass, or swelling
- Hematuria, fever
- Hypertension
- Genitourinary malformations
- Aniridia, hemihypertrophy

**CLINICAL FEATURES (FIG. 1)**

The most common initial clinical presentation is the mass can be quite large because retroperitoneal masses can grow unhampered by strict anatomic boundaries. The child may present with mass in abdomen. Pain in the abdomen or hematuria are rarely seen. Aniridia and hemihypertrophy may be associated. Cataract, genitourinary abnormalities and mental retardation are present. A nontender mass is palpable in the renal area. It generally does not cross the midline. At time mass is pushed. Hypertension is present in approximately 25% of tumors at presentation and has been attributed to increased renin activity. Palpation should be gentle and minimum to obviate the spread of metastasis.

Abdominal pain, gross painless hematuria, and fever are other frequent findings at diagnosis. Occasionally, rapid abdominal enlargement and anemia occur as a result of bleeding into the renal parenchyma or pelvis.

The classic presentation of a child with WT is the discovery of an abdominal mass by a parent bathing or dressing the child or by the pediatrician on a routine well-child visit. Symptoms can include constipation, abdominal pain and/or distension, and hematuria, but the patient can

also be asymptomatic. Clinical signs can include hypertension and anemia. Rarely, spontaneous rupture of a WT can occur, leading to sudden pain and anemia due to bleeding within and surrounding the tumor. The majority of WT cases are unilateral, affecting only 1 kidney. Bilateral WT comprises 7% of total cases and is more common in individuals with genetic predisposition syndromes.

**GENERAL FEATURES**

- Hemihypertrophy
- Genitourinary abnormalities

**DIAGNOSIS**

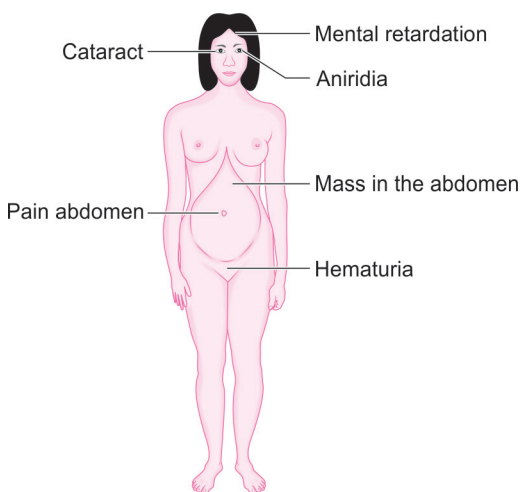
Patients with a suspected renal mass should have a complete blood count and differential, a full electrolyte panel, blood urea nitrogen and creatinine (to evaluate kidney function), and liver function tests. Coagulation studies and a type and screen should be done prior to surgical intervention since WT has been associated with acquired von Willebrand disease, a bleeding disorder that affects primary hemostasis. Urinalysis may reveal hematuria, and urine catecholamine levels will be negative in WT and positive in most cases of neuroblastoma. These findings can help distinguish these two abdominal tumors, which occur in similar age groups.

It should be considered as an emergency. Intravenous pyelography (IVP) shows distortion of renal pelvis with or without minimum displacement. Plain radiograph shows unilinear calcifications. Resection is undertaken as soon as possible.

Regional lymph nodes with slightest suspicion should be removed. Preoperative irradiation is not recommended because it induces fibrosis and makes resection difficult.

Ultrasonography with Doppler imaging of renal veins and the inferior vena caval is a useful first study that not only can look for WT but also can evaluate the collecting system and demonstrate tumor thrombi in the renal veins and inferior vena cava.

Although US is helpful in diagnosing the presence of a renal tumor, subsequent cross-sectional imaging with magnetic resonance imaging (MRI) or computed tomography (CT) is necessary to define better the anatomy of the tumor and to aid in surgical planning. The classic finding consistent with WT on cross-sectional imaging is the "claw sign" in which the tumor displaces



**Fig. 1:** Clinical features.

normal kidney tissue, giving the appearance of tumor surrounded by a claw of normal kidney tissue. CT is the most commonly used imaging modality for initial staging of pediatric renal tumors because of its easy accessibility and short duration; however, some institutions have been using MRI to spare the patients exposure to ionizing radiation.

Computed tomography is useful to define the extent of the disease, integrity of the contralateral kidney, and metastasis. MRI is may be helpful in defining an extensive tumor thrombus that extends up to the level of the hepatic veins or even into the right atrium, and to distinguish WT from nephrogenic rests.

Chest CT is more sensitive than chest radiography to screen for pulmonary metastasis, and is preferable performed before surgery because effusions and atelectasis can interpretation of postoperative imaging studies. Liver scan is done to look for hepatic metastasis.

A bone scan is performed if the histologic diagnosis confirms clear cell sarcoma of the kidney to look for bone metastasis. Brain imaging with CT or MRI is obtained in cases of clear cell sarcoma of the kidney or rhabdoid tumor of the kidney as these tumors can spread to the brain.

Investigation	Purpose
Abdominal USG	<ul style="list-style-type: none"> <li>• Organ of origin</li> <li>• Identify contralateral kidney</li> <li>• Presence/absence of tumor thrombus in IVC</li> </ul>
CT scan	<ul style="list-style-type: none"> <li>• Further evaluation of extent of tumor</li> <li>• Extension into adjoining structures such as liver spleen and colon</li> <li>• Visualization and function of contralateral kidney</li> </ul>
Chest X-ray	Pulmonary metastasis
Bone scan and skeletal survey	Bone metastasis in clear cell sarcoma of kidney
Brain imaging (MRI/CT scan)	Intracranial metastasis in rhabdoid tumor (RT)
Fine-needle aspiration cytology of mass	Cytological confirmation of diagnosis prior to prenephrectomy chemotherapy

On microscopic examination, muscle fibers, abortive glomeruli and undifferentiated spindle-like mesenchymal cells encloses epithelial lining tubules. Prognosis is better in tumor with dominance of epithelial components.

## NATIONAL WILMS' TUMOR STUDY (NWTs) STAGING

This is a clinicopathologic staging system.

- Stage I:** Tumor confined to the kidney and completely excised
- Stage II:** Tumor extending beyond the kidney but is completely excised  
Local tumor spillage during surgery  
Lymph nodes negative
- Stage III:** Residual nonhematogenous disease confined to the abdomen  
Perioperative rupture of renal capsule  
Diffuse tumor spillage during surgery  
Peritoneal implants  
Positive lymph nodes
- Stage IV:** Hematogenous metastases to lungs, liver, bones or brain
- Stage V:** Bilateral Wilms tumor

The differential diagnosis of WT includes benign processes such as renal cysts, dysplastic kidneys, a renal abscess, or other renal malignancies. Neuroblastoma should also be considered because WT and neuroblastoma occur in the same age group and affect adjacent organs of the abdomen: WT arises from the kidney and neuroblastoma arises from the adrenal gland. Lymphoma involving the kidneys can masquerade as a renal tumor. Finally, benign renal tumors such as cystic nephroma, metanephric tumors, and cystic partially differentiated nephroblastoma should be included in the differential diagnosis. Age of presentation, clinical and laboratory features, and imaging appearance may provide clues to the diagnosis, but histologic assessment remains the gold standard for diagnosis.

## DIFFERENTIAL DIAGNOSIS

- Neuroblastoma
- Leukemia
- Hydronephrosis
- Pyelonephritis
- Multicystic disease of kidney

## TREATMENT

All the three modalities of treatment including surgery, chemotherapy and radiotherapy. The immediate treatment for unilateral disease is removal of affected kidney. Many prefer preoperative chemotherapy because it diminishes the size of the tumor and makes it possible to come to better tumor staging. Actinomycin D and vincristine are used for 4 weeks. Commonly used drugs are vincristine, actinomycin D and adriamycin.

Surgical removal of the primary tumor is a cornerstone of WT treatment. Regardless of surgical timing (prior to or after chemotherapy), radical nephrectomy is recommended for unilateral WT. A transverse abdominal incision is generally used as it is important to avoid tumor rupture, which has been associated with increased risk of local recurrence. Regional lymph node sampling is also performed to ensure optimal staging. Partial nephrectomy is recommended for patients with bilateral WT to spare as much normal renal parenchyma as possible.

After nephrectomy and lymph node sampling, chemotherapy and radiotherapy depends upon the stages:

- Stage I and II (Favorable histology) and stage I (focal or diffuse anaplasia). Nephrectomy and 18 weeks of chemotherapy with vincristine and pulse intensive dactinomycin.
- Stage II, III and IV (Focal anaplasia). Nephrectomy, abdominal irradiation (10 Gy) and 24 weeks of chemotherapy with vincristine, doxorubicin, and pulse intensive dactinomycin.
- Stage I-IV (Clear cell) and stage II-IV (diffuse anaplasia). Nephrectomy, radiotherapy (10 Gy) for abdomen (12 Gy) for lungs 24 weeks of chemotherapy with vincristine, doxorubicin, cyclophosphamide and VP-16.
- Stage I-IV (Rhabdoid). Nephrectomy, radiotherapy, carboplatin, VP 16 and cyclophosphamide.

Actinomycin D in the dose of 15 µg/kg is given intravenously for 5 consecutive days from day 1. The course is repeated after 6, 12, 25, 38, 51 and 64 weeks.

Vincristine is given in a dose of 1.5 mg/m<sup>2</sup>, or a maximum of 2 mg, intravenously once a week for 8–12 weeks. Cyclophosphamide in high doses for tumor regression is recommended. Adriamycin also gives good results.

Doxorubicin and abdominal radiation are additional therapies for stage III illness. Cyclophosphamide, carboplatin and etoposide are used for anaplasia and metastatic disease. Pulmonary radiation is used for pulmonary metastasis.

Bilateral tumors and tumors considered inoperable at first surgery should receive 4–6 weeks of chemotherapy followed by second look surgery. In case of bilateral tumors, effort should be made to preserve as much of each kidney as possible. In such cases, chemotherapy may have to be given for a longer period to enable partial nephrectomy to be done.

## Prenephrectomy Chemotherapy

It helps to decrease the need for postoperative abdominal radiation therapy in event of tumor rupture during nephrectomy. Risks of prenephrectomy chemotherapy include modification of tumor histology and loss of staging information.

### *Absolute Indications for Prenephrectomy Chemotherapy*

- Large tumor technically difficult to deliver at surgery
- Presence of major tumor thrombus in the inferior vena cava
- Bilateral Wilms' tumor
- Wilms' tumor in a solitary kidney or horse shoe kidney

## Radiotherapy for Wilms' Tumor

### *Indications*

- Stage II unfavorable histology
- Stage III favorable and unfavorable histology
- Stage IV lung bath for pulmonary metastases. Need for RT to tumor bed is determined by local stage
- Local recurrence
- Palliative radiotherapy for metastatic disease

### *Principles of Radiation Therapy*

Radiotherapy is very effective in the treatment of WT; however, its use is reserved for higher-stage FH WT or AH WT due to the risk of acute and long-term toxicities. Patients with local stage II WT receive either flank or whole abdominal radiation, depending on the local extent of spread.

Radiotherapy should be planned starting within 10 days of surgery. No change of radiotherapy dose for favorable and unfavorable histology.

### *Target Volume*

Volume should encompass tumor bed and site of excised kidney with 2–3 cm margin. Entire vertebral body to be encompassed to avoid disproportionate growth.

### *Special Considerations*

In patients with stage V, or bilateral disease, an initial 6–12 weeks of chemotherapy precedes surgery in order to optimize tumor shrinkage prior to nephron-sparing surgery or partial nephrectomy. This is done in order to preserve as much renal function as possible.

Treatment of recurrent WT has improved over time with the introduction of new active chemotherapy drugs. The most important prognostic factor at the time of recurrence is the therapy that was administered for the original WT treatment. Patients treated initially with just vincristine and dactinomycin have an 80% survival rate after recurrence, whereas patients treated initially with three or more agents have a 50% survival rate after recurrence. The role of high-dose therapy with autologous stem cell rescue has been the subject of considerable debate. Although a randomized clinical trial to assess the benefit of high-dose therapy has not been conducted, a meta-analysis of the available literature suggested that the benefit of high-dose therapy is restricted to patients who received more than four agents as part of their initial treatment.

## CONCLUSION

Since WT is one of the most curable malignancies of childhood, special emphasis needs to be laid on the need for surveillance for late effects of development, fertility and second malignant neoplasm.

## PROGNOSIS

Prognostic factors are determined by staging. Another factor is pathology. Tumor with favorable

pathology have better prognosis and require only surgical excision. Tumor with unfavorable histology, i.e., bone metastasis, pleomorphic and ruptured have poor prognosis. They require intensive therapy. Tumor with standard histology, treatment has to be adjusted to staging. Ploidy is another prognostic sign, diploid tumors have a better prognosis than hyperdiploid tumor.

Anaplastic histology (focal and diffuse) accounts for approximately 11% of WT cases. Patients with diffuse anaplasia, in particular have a poor outcome. They are treated with intensive chemotherapy regimens [fiat include vincristine, cyclophosphamide, doxorubicin, etoposide, loba-platin, and ifosfamide, in addition to radiation therapy.

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# Acute Rheumatic Fever

## PRESENTING COMPLAINTS

A 7-year-old girl was brought with the complaints of:

- Sore throat since 15 days
- Pain in the joint since 10 days
- Palpitation since 7 days
- Fever since 5 days

## History of Presenting Complaints

A 7-year-old girl came with the history of pain in left knee joint. Mother noted that there was swelling of the joint. The swelling was very painful and not allowing her to move her leg. She also complained of similar type of pain in the left shoulder. Girl also told that the pain in the left shoulder joint has disappeared by the time she noticed pain in left knee joint. There was also associated history

of fever. Fever used to be of moderate to high degree. There was no history of chills and rigors. Fever used to be more in the evening and night. Girl also complained of abnormal awareness of the heartbeat. She used to feel much tired even for the routine work.

## Past History of the Patient

She was the only sibling of nonconsanguineous marriage. She was born at full term by normal vaginal delivery. Her birth weight was 3 kg. She cried immediately after the delivery. There was no significant postnatal event. She was exclusively on the breastfeeds for first 3 months. Later weaning was started as per the advice of the family doctor and the child was on family food by 18 months. Her developmental milestones were normal. She had been completely immunized. Her performance at the school was good.

Mother complained that her daughter used to develop repeated attack of throat pain, for which she was seeking medical treatment. She was getting pain in the joints occasionally.

## CASE AT A GLANCE

### Basic Findings

Height	: 117 cm (50th centile)
Weight	: 19 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 116 per minute
Respiratory rate	: 24 per minute
Blood pressure	: 90/60 mm Hg

### Positive Findings

#### History

- Fleeting type of joint pain
- Fever
- Sore throat
- Palpitation

#### Examination

- Febrile
- Arthritis
- Diastolic murmur
- Loud first heart sound

#### Investigation

- Hemoglobin: 9 g/dL
- ESR: Raised
- Chest X-ray: Cardiomegaly
- ASLO: Raised
- CRP: Raised
- ECG: Prolonged P-R interval

## EXAMINATION

On examination, the girl was moderately built and moderately nourished. She was in agony with pain in the joint. Her anthropometric measurement included, her height was 117 cm (50th centile), the weight was 19 kg (50th centile).

She was febrile, i.e., 38°C, the pulse rate was 116 per minute, the respiratory rate was 24 per minute. Blood pressure recorded was 90/60 mm Hg.

There was pallor, no lymphadenopathy, and no cyanosis. There was pain and swelling in the left knee joint. There were limitations of the movements.

Cardiovascular system revealed presence of diastolic thrill at the apex associated with the mid-diastolic murmur at the apex. The first heart sound was loud. Second heart sound was normal. Respiratory system revealed presence of crepitation at the base. Per abdomen examination revealed no significant abnormality.



## INVESTIGATION

Hemoglobin	: 9 g/dL
TLC	: 7,600 cells/cu mm
DLC	: P <sub>72</sub> L <sub>18</sub> M <sub>2</sub> E <sub>6</sub> B <sub>2</sub>
ESR	: 28 mm in the 1st hour
X-ray chest	: Cardiomegaly
ASLO	: 400 Todd units
CRP	: 1100 µg/dL (Normal range: 67–1000 µg/dL)
Throat culture and sensitivity	: Sterile
Blood culture and sensitivity	: Sterile
ECG	: P-R interval is prolonged, right ventricular hypertrophy seen

## DISCUSSION

Rheumatic fever is a multisystem disease, triggered by Group A beta-hemolytic *Streptococcus*. Its acute manifestations include arthritis, carditis, chorea, subcutaneous nodules and erythema marginatum. It is recurrent in nature and results in chronic heart disease. Hence, it is said rheumatic fever licks the joints and bites the heart.

Acute rheumatic fever (ARF) is a nonsuppurative sequela of pharyngeal infection with group A *Streptococcus* (GAS). Target organs of the resultant autoimmune process include the heart, joints, central nervous system, and subcutaneous tissues. Permanent cardiac damage is the most important consequence of this disease.

Acute rheumatic fever is an immunological disorder. This is initiated by Group A beta-hemolytic streptococci. Antibodies produced against the streptococcal protein and sugar react against the connective tissue of the body as well as heart. This results in rheumatic fever.

Predisposing factors include poor socioeconomic condition leading to unhygienic living condition and over crowded house holds. Under and poor nutrition will alter the immune system.

The most common age involved is 5–15 years. Mitral valve disease and chorea are common in female. Aortic valve involvement is common in males. Rheumatic fever occurs during winter season.

As many as two-thirds of patients with an acute episode of rheumatic fever have history of an upper respiratory tract infection several weeks before, and the peak age and seasonal incidence of acute rheumatic fever closely parallel that of GAS pharyngitis. Patients with acute rheumatic fever

almost always have serologic evidence of a recent GAS infection. Their antibody titers are usually considerably higher than those seen in patients with uncomplicated GAS infections.

Rheumatic fever follows an attack of streptococcal infection of upper respiratory tract and usually there will be laboratory evidence of recent streptococcal infection. The latent period of rheumatic fever is 1–3 weeks and that of chorea is 2–6 months. The major epidemiological risk factor for the development of acute RF is group A β-hemolytic streptococcal infection of the upper respiratory tract. Almost all serotypes of streptococci are involved.

Not all serotypes of GAS can cause rheumatic fever. When some GAS strains (e.g., M type 4) causes acute pharyngitis in a very susceptible rheumatic population. Certain serotypes of GAS (M types 1, 3, 5, 6, 18, 29) are more frequently isolated from patients with acute rheumatic fever than are other serotypes.

In addition to the specific characteristics of the infecting strain of GAS, the risk of developing acute rheumatic fever is also dependent on various host factors. The incidence of both initial attacks and recurrences of acute rheumatic fever peaks in children 5–15 years of age, the age of greatest risk for GAS pharyngitis. Patients who have had an attack of acute rheumatic fever tend to have recurrences, and the clinical features of the recurrences tend to mimic those of the initial attack. In addition, there appears to be a genetic predisposition to acute rheumatic fever.

The streptococcal cell wall proteins as well as carbohydrates have the capacity to produce antibodies capable of reacting with human connective tissue resulting in rheumatic fever. It appears to be the result of host's unusual response at both the cellular and humoral level to the *Streptococcus*. Antibodies against the heart muscle antiheart antibodies and the nervous system, antineuronal antibodies are found in high titers with carditis and chorea.

An immune-mediated pathogenesis for acute rheumatic fever and rheumatic heart disease has been suggested by its clinical similarity to other illnesses with an immunopathogenesis and by the latent period between the GAS infection and acute rheumatic fever. The antigenicity of several GAS cellular and extracellular epitopes and their immunologic cross-reactivity with cardiac antigenic epitopes also lends support to the hypothesis of molecular mimicry.

Common epitopes are shared between certain GAS components (e.g., M protein, cell membrane,

group A cell wall carbohydrate, capsular hyaluronate) and specific mammalian tissues (e.g., heart valve, sarcomere, brain, joint). Additionally, the involvement of GAS superantigens such as pyrogenic exotoxins in the pathogenesis of acute rheumatic fever has been proposed.

A more recently proposed pathogenetic hypothesis is that the binding of an M protein N-terminus domain to a region of collagen type IV leads to an antibody response to the collagen, resulting in ground substance inflammation especially in subendothelial areas like cardiac valves and myocardium.

## **PATHOLOGY**

Acute rheumatic fever occurs most often in the winter and spring seasons and in children ages 5–15 years. Much less commonly, it has been reported in the preschool age group. Patients with ARF have a high likelihood of recurrence when reinfected with GAS; this tendency declines with age and age increased time since the last episode. Environmental factors such as nutrition, wading, and age all appear to influence the incidence of ARF, probably because the same factors influence the incidence of streptococcal pharyngitis.

Antigenic differences among GAS serotypes are related to the bacterial M protein, found within its cell wall. Recent data demonstrated a shift in prevalence from ‘rheumatogenic’ to ‘nonrheumatogenic’ M types over the past 40 years that parallels the decrease in the incidence of ARF over this period. The 10 days to 3 weeks period between streptococcal pharyngitis and ARF is consistent with a cellular and humoral immune response. Cross-reactivity of streptococcal antigens and human cardiac, synovial, and brain antigens also supports an immune mechanism of ARF.

Pathologic changes are found throughout the body in connective tissue and around small blood vessels. The pathognomonic lesion of rheumatic fever is the Aschoff body, a painless nodular connective tissue lesion consisting of fibrinoid changes and a collection of lymphocytes, plasma cells, and histiocytes. Within the heart, the endocardium and myocardium are most often affected; the pericardium involved by extension or as serositis. Active valvulitis results in variable degrees of valve insufficiency, with chronic changes possibly leading to valvar stenosis. The mitral and aortic valves are affected most commonly, the tricuspid less frequently, and the pulmonary valve rarely.

Pathologic changes in the joints consist of joint effusion, exudation with edema of synovial

membranes, focal necrosis in the joint capsule, and edema and inflammation in periarticular tissue. These changes are completely reversible. Subcutaneous nodules seen during the acute phase of the disease histologically resemble Aschoff bodies.

The pathological process is described in two stages:

1. Exudative stage
2. Proliferative stage

### **Exudative Stage**

In this acute phase, there is fibrinoid necrosis of connective tissues with edema of collagen fibers, resulting in two major clinical signs.

1. *Arthritis*: Without residuals
2. *Pancarditis*: It is a life-threatening condition

### **Proliferative Stage**

It is a more prolonged process, resulting in scarring of myocardium and endocardium. During ARF, Aschoff bodies involve all the layers to produce pancarditis. The hallmark of the proliferative phase is the formation of Aschoff bodies. These are granulomas due to injury to collagen. Other important event is deposition of gamma globulins in heart. Lesion in pericardium is a fibrinous inflammation and macroscopically shows a ‘bread and butter’ appearance. Endocarditis affects the valvular or mural endocardium. When the valvular endocardium heals, it results in scarring and deformity of valves. The valves damaged usually are mitral, aortic, tricuspid and pulmonary.

## **CLINICAL FEATURES (FIG. 1)**

The classical clinical picture of rheumatic fever includes streptococcal sore throat with fever. Rheumatic fever is diagnosed depending upon presence of criteria. Criteria may be major or minor. Major criteria include carditis, subcutaneous nodules, chorea and erythema marginatum. The minor criteria include fever, arthralgia, anti-streptolysin O (ASLO) titer value, positive throat culture, acute phase reactions and prolonged P-R interval.

Diagnosis requires that an individual have either two major criteria or one major criterion plus two minor criteria along with evidence of streptococcal infection. Exceptions are chorea or indolent carditis, which each may by itself indicate rheumatic fever.

The essential criteria include evidence of recent streptococcal infections such as raised ASLO titer and positive throat culture.

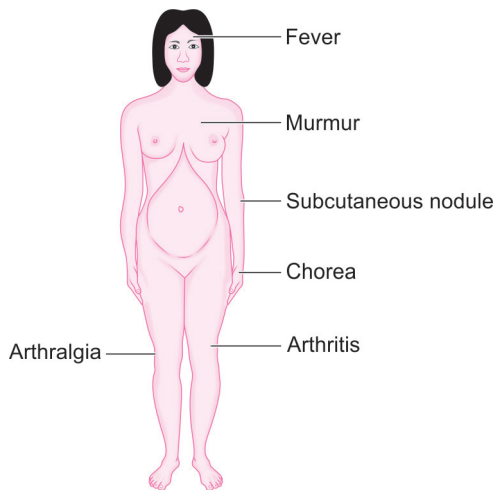


Fig. 1: Clinical features.

ESSENTIAL DIAGNOSTIC POINTS

- Migratory polyarthritis
- Carditis
- Sydenham's chorea
- Evidence streptococcal infection such as scarlet fever, positive throat culture, ASLO titer
- Acute phase reactants are elevated
- EEG changes

CLINICAL MANIFESTATIONS AND DIAGNOSIS

There is no single specific clinical manifestation or specific laboratory test that establishes the diagnosis. There are number of selective clinical findings (Jones criteria) that make diagnosis of rheumatic fever highly probable. The revised Jones criteria are described below:

Major criteria	Minor criteria
<ul style="list-style-type: none"><li>• Carditis</li><li>• Polyarthritis migratory</li><li>• Erythema marginatum</li><li>• Chorea</li><li>• Subcutaneous nodules</li></ul>	<ul style="list-style-type: none"><li>• Fever</li><li>• Arthralgia</li><li>• Previous history of rheumatic fever</li><li>• Elevated acute phase</li><li>• Phase reactants (ESR, CRP)</li><li>• Prolonged P-R interval on an ECG</li></ul>
Plus (essential criteria)	
Evidence of a preceding group A streptococcal infection (culture, rapid raise in antigen-antibody titer)	

The presence of two major criteria or one major and two minor criteria indicates a high probability of the presence of rheumatic fever. Evidence of preceding streptococcal infection greatly strengthens the possibility of ARF. Its absence should

make the diagnosis doubtful, except of Sydenham's chorea or long-standing carditis.

The *Jones criteria*, as revised in 2015, is now intended for diagnosis of the initial attack of ARF and recurrent attacks. There are five major and four minor criteria and a requirement of evidence of recent GAS infection.

Migratory Polyarthritis

In rheumatic fever, 60–70% suffer from acute arthritis. Arthritis, the early manifestation of rheumatic fever lasts for 3–7 days and leaves no residual damage. It is polyarthritis involving the large joints such as knee, ankles, and elbows. Acute arthritis affecting the major joints is the characteristic involvement. The joints show signs of acute inflammation grade IV tenderness and limitation of movements. The arthritis is migratory and fleeting and leaves behind no residual changes.

Arthritis occurs in approximately 75% of patients with ARF and typically involves larger joints, particularly the knees, ankles, wrists, and elbows. Involvement of the spine, small joints of the hands and feet, or hips is uncommon. Rheumatic joints are classically hot, red, swollen, and exquisitely tender, with even the friction of bedclothes being uncomfortable. The pain can precede and can appear to be disproportionate to the objective findings. The joint involvement is characteristically migratory in nature; that is, a severely inflamed joint can become normal within 1–3 days without treatment, even as one or more other large joints become involved. Severe arthritis can persist for several weeks in untreated patients. Polyarthritis is the most common of the major criteria and lasts less than 4–6 weeks when untreated. Characteristic is a dramatic response to salicylates and nonsteroidal anti-inflammatory drugs (NSAIDs); early use in febrile children may confound diagnosis.

Carditis

A major change in the Jones criteria is the acceptance of subclinical carditis (defined as without a murmur of valvulitis but with echocardiographic evidence of valvulitis) or clinical carditis (with a valvulitis murmur) as fulfilling the major criterion of carditis in all populations.

Acute rheumatic carditis usually presents as tachycardia and cardiac murmurs, with or without evidence of myocardial or pericardial involvement. Moderate to severe rheumatic carditis can result

in cardiomegaly and heart failure with hepatomegaly and peripheral and pulmonary edema. Echocardiographic findings are not diagnostic but include pericardial effusion, decreased ventricular contractility, and aortic and/or mitral regurgitation.

Mitral regurgitation is characterized typically by a high-pitched apical holosystolic murmur radiating to the axilla. In patients with significant initial regurgitation, this may be associated with an apical mid-diastolic murmur of relative mitral stenosis. Aortic insufficiency is characterized by a high-pitched decrescendo diastolic murmur at the left sternal border.

Carditis occurs in approximately 50–60% of all cases of ARF. Recurrent attacks of ARF in patients who had carditis with their initial attack are associated with high rates of carditis with increasing severity of cardiac disease. The major consequence of acute rheumatic carditis is chronic, progressive valvular disease, particularly valvular stenosis, which can require valve replacement. In developing countries, 60–80% cases of rheumatic fever have clinical features of carditis and in 40% is seen during the first attack of rheumatic fever.

It is pancarditis involving pericardium, myocardium and endocardium. Carditis occurs within 2 weeks of the onset of the fever. It is an early manifestation of the rheumatic fever so that by the time a patient seeks help, he had already had carditis.

Pericarditis may appear suddenly and may be associated with precordial pain and a friction rub. More often, however, patients with pericarditis are asymptomatic. Pericarditis seldom appears without endocarditis and myocarditis, the combination being termed pancarditis. Death may occur during the acute phase of carditis; permanent cardiac damage may result in long-term disability, usually because of mitral or aortic valvar insufficiency and/or stenosis. Pericarditis results in pericardial pain. The pain may be quite severe. Friction rub may be heard on auscultation. ECG shows ST and T wave changes. A patient of rheumatic pericarditis always has additional mitral or mitral and aortic regurgitation murmur. Myocarditis presents with cardiac enlargement, soft heart sound and congestive cardiac failure (CCF). Carey Coombs murmur is a delayed diastolic mitral murmur heard during the course of ARF. S3 gallop may be present. Gallop rhythm is an abnormal array of heart sounds in which third and fourth heart sound may also be present, and usually indicates active disease of the heart. Arrhythmias are present.

Endocarditis (valvulitis) is represented by pansystolic murmur of mitral regurgitation. Tricuspid valvulitis results in tricuspid regurgitation. The severity of the valvular endocarditis causes acute or later chronic hemodynamic overload. Acute hemodynamic overload is the main reason of morbidity and mortality of the rheumatic fever. The most frequent murmur is an apical regurgitant systolic murmur of mitral regurgitation. With severe mitral regurgitation, the third heart sound may be followed or replaced by a low-pitched mid-diastolic rumble. The early diastolic murmur of aortic regurgitation is the second most common murmur in ARF and generally occurs only in patients who also have mitral regurgitation.

Cardiomegaly may be evident on radiograph. Severe myocarditis may result in congestive heart failure with signs including jugular-venous distention, hepatomegaly, and pulmonary edema with rales. Prolongation of the P-R demonstrated on an electrocardiogram interval is common but does not indicate carditis.

### *Clinical Features of Carditis*

- Murmurs
  - Significant apical systolic murmurs (Musical quality of grade III)
  - Apical mid-diastolic murmur due to edema of valve (Carey-Coombs murmur)
  - Basal diastolic murmur
- Enlarged heart
- Congestive heart failure
- Presence of pericardial rub

Others include:

- Tachycardia (sleeping)
- Heart sounds (decreased or muffled)
- Gallop, arrhythmias, changing murmurs
- Subcutaneous nodules
- Persistent dry cough, ECG changes lab findings raised ESR and presence of CRP
- Valves affected in frequency of occurrence are, mitral 70%, mitral and aortic (7%), tricuspid and pulmonary valves are rarely affected

### **Subcutaneous Nodules**

They appear as early as 6 weeks after the onset of fever. These lesions are very infrequent and are present in 1–10% of patients with rheumatic fever. Nodules are better seen than felt. They are firm nontender, pea-sized nodules seen over the extensor aspects of forearm, elbows, wrist, knees, ankles, spine, scalp and along tendons. The presence of rheumatic nodules indicates presence of

activity in 100% of cases and underlying carditis in 70% of cases. Subcutaneous nodules are a rare (<1% of patients with ARF) finding and consist of firm nodules approximately 1 cm in diameter along the extensor surfaces of tendons near bony prominences. There is a correlation between the presence of these nodules and significant rheumatic heart disease.

## Chorea

Chorea occasionally is unilateral (hemichorea). The latent period from acute GAS infection to chorea is usually substantially longer than for arthritis or carditis and can be months. Onset can be insidious, with symptoms being present for several months before recognition. Sydenham chorea occurs in approximately 10–15% of patients with ARF and usually presents as an isolated, frequently subtle, movement disorder, emotional lability, incoordination, poor school performance, uncontrollable movements, and facial grimacing all exacerbated by stress and disappearing with sleep, are characteristic.

Sydenham chorea is characterized by sudden, aimless, irregular movements of the extremities frequently associated with emotional instability and muscle weakness. Whereas carditis and arthritis develop within weeks after an inciting streptococcal infection, chorea presents after several months and is not often associated with other features of ARF except perhaps mild carditis. The onset may be gradual complaints that the child is nervous. The child may become clumsy and stumble, fall, or drop objects. Often there are complaints of poor attention and deteriorating handwriting and school performance. Facial grimacing and various speech disorders occur. As chorea becomes more severe, irregular jerking movements can be sufficiently violent to cause injuries. Muscle weakness may be profound.

The choreiform movements subside during sleep and are exaggerated by emotion. Characteristically, when the patient is asked to extend the arms, hands, and fingers, flexion of the wrists and hyperextension of the metacarpophalangeal joints (“silver forking”) are observed. The pronator sign may be elicited: alter the arms are raised above the head, there is gradual pronation of the hands (apposition of the dorsal aspects of the hands). Other signs are an inability to hold the tongue still when it is protruded and spasmodic contractions of the hands when the patient intentionally grips objects or the examiner’s hand (milkmaid’s grip).

Chorea can also be caused by diseases other than ARF, such as systemic lupus erythematosus (SLE) or Wilson disease and patients who present with chorea as the only manifestation of ARF should undergo a full evaluation.

Chorea develops much later than other manifestation of rheumatic fever and 25% of these cases develop carditis after 10 years. This appears 3 months after onset of the fever. It consists of purposeless jerky movements, resulting in deranged speech, muscular incoordination, awkward gait and weakness. It is more common among female. It is self-limiting disease. The duration of illness is 2–6 weeks.

## Erythema Marginatum

These are erythematous nonpruritic annular lesions with serpiginous borders, usually seen over the anterior aspects of chest, abdomen and thigh. It is more specific. The rash is more faintly reddish, not raised above the skin. Erythema marginatum occurs in less than 10% of ARF patients; it may be seen *more frequently in children* less than 5-year-old. The characteristic rash consists of an evanescent, pink, erythematous macule, with a clear center and serpiginous outline. The rash is transient, migratory, and not pruritic; it blanches with pressure, is exacerbated by warmth. It occurs primarily on the trunk and extremities, but not on the face, and it can be accentuated by warming the skin.

## Minor Criteria

- *Clinical*
  - Fever
  - Arthralgia
- Laboratory evidence
  - Acute phase reactants
    - ♦ Polymorphonuclear reactants
    - ♦ ESR raised
    - ♦ CRP is raised
    - ♦ Prolonged P-R interval

The two laboratory minor criteria are (1) elevated acute phase reactants (defined as ESR at least 60 mm/h and/or CRP at least 3.0 mg/dL [30 mg/L] in low-risk populations, and ESR at least 30 mm/h and/or CRP at least 3.0 mg/dL [30 mg/dL] in moderate/high-risk populations) and (2) prolonged P-R interval on ECG (unless carditis is a major criterion). However, a prolonged P-R interval alone does not constitute evidence of carditis or predict long-term cardiac sequelae.



## Recent Group A *Streptococcus* Infection

An absolute requirement for the diagnosis of ARF is supporting evidence of a recent GAS infection. ARF typically develops 2–4 weeks after an acute episode of GAS pharyngitis at a time when clinical findings of pharyngitis are no longer present. One-third of patients with ARF have no history of an antecedent pharyngitis. Therefore, evidence of an antecedent GAS infection is usually based on elevated or rising serum antistreptococcal antibody titers.

If only single antibody is measured (usually ASLO), only 80–85% of patients with ARF have an elevated titer; however, 95–100% have an elevation if three different antibodies (ASLO, anti-DNase B, antihyaluronidase) are measured. Therefore, when ARF is suspected clinically, multiple antibody tests should be performed. Except for chorea, the clinical findings of ARF generally coincide with peak antistreptococcal antibody responses. Most patients with chorea have elevation of antibodies to at least GAS antigen. The diagnosis of ARF should not be made in those patients with elevated or increasing streptococcal antibody titers who do not fulfill the Jones criteria.

### GENERAL FEATURES

- Carditis
- Fever
- Erythema marginatum
- ASLO titer

## Laboratory Diagnosis of Rheumatic Fever

Proof of previous streptococcal infection is required in addition to combinations of major and minor criteria. Paired, increasing serum antistreptococcal antibody titers are probably the most specific and reliable proof of previous streptococcal infection. A rising antibody titer to specific streptococcal antigens is more specific than a single elevated value. However, if the patient presents with chorea more than 3 months after the acute streptococcal infection, then antibody titers may be declining or low. The most widely used serologic test is antibody formation against streptolysin O. Titers of at least 333 U in children and 250 U in adults are usually considered elevated.

Acute phase reactants like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are always elevated at the onset of rheumatic fever. There may be neutrophilic leukocytosis and anemia.

- Serial chest X-rays are required to assess the progressive cardiac enlargement

- ECG shows conduction defects and signs of carditis and pericarditis

Preceding streptococcal infections are confirmed by following tests:

**Throat culture:** This remains the gold standard for confirmation of presence of group A streptococci and 25–40% of the individuals have positive throat culture.

**Serodiagnosis:** ASLO titer has been the widely accepted diagnostic test for rheumatic fever. A titer of 333 Todd units and above is suggestive of ARF.

Other Streptococcal antigens tested are:

- Antistreptokinase
- Antihyaluronidase
- Anti-DNase B

### LABORATORY SALIENT FINDINGS

- *Elevated acute phase reactants:* Raised ESR, C-reactive protein, leukocytosis
- Rise in ASLO titer
- Chest X-ray
- ECG changes

## DIFFERENTIAL DIAGNOSIS

- Juvenile rheumatoid arthritis
- Lyme disease
- Osteomyelitis
- Pharyngitis
- Viral fever

## TREATMENT

Treatment of rheumatic fever may be divided into three stages:

1. Management of acute stage
2. Eradication of streptococcal infection
3. Prevention of recurrence

### Management of Acute Stage

Arthritis, carditis and Sydenham's chorea are the three acute systemic manifestation of ARF. So the acute therapy is planned, at the management of these three conditions.

Strict bed rest is advised for all three conditions.

Mainstay of the treatment is strict bed rest especially when there is evidence of carditis is present. Bed rest is advised till the evidence of the activity subsides. Salt restriction is advised in congestive cardiac failure associated with carditis. Throat culture and sensitivity test should be done. Procaine penicillin 4 units given for 10 days. This may be followed by prophylactic penicillin.

If a child with ARF is free of clinical carditis, normal activity can be resumed once the pain and

fever resolve. There is mild carditis, a period of 1–2 weeks resting at home is reasonable. The murmur may persist indefinitely, and its disappearance is not a requisite for return to activity. The ESR may remain high or weeks, showing gradual decline. All patients with ARF should be placed on bed rest and monitored closely for evidence of carditis. However, patients with carditis require longer periods of bed rest.

### *Anti-inflammatory Therapy*

Anti-inflammatory agents (e.g., salicylates, corticosteroids) should be withheld if arthralgia or atypical arthritis is the only clinical manifestation of presumed acute rheumatic fever. Acetaminophen can be used to control pain and fever while the patient is being observed for more definite signs of ARF or for evidence of another disease.

Patients with typical migratory polyarthritis and those with carditis without cardiomegaly or congestive heart failure should be treated with oral salicylates. The usual dose of aspirin is 50–70 mg/kg/day in four divided doses PO for 3–5 days, followed by 50 mg/kg/day in four divided doses PO for 3 weeks and half that dose for another 2–4 weeks. If rebound of rheumatic activity occurs, full therapy may have to be reinstituted for an additional 4–6 weeks.

Patients with carditis and more than minimal cardiomegaly and/or congestive heart failure should receive corticosteroids. The usual dose of prednisone is 2 mg/kg/day in four divided doses for 2–3 weeks followed by half the dose for 2–3 weeks and then tapering of the dose by 5 mg/24 h every 2–3 days. When prednisone is being tapered, aspirin should be started at 50 mg/kg/day in four divided doses for 6 weeks to prevent rebound of inflammation. Supportive therapies for patients with moderate to severe carditis include digoxin, fluid and salt restriction, diuretics, and oxygen. The cardiac toxicity of digoxin is enhanced with myocarditis.

In patients with moderate to severe carditis, neither salicylates nor steroids demonstrate superiority over the other drug in modifying the duration of acute disease or lessening the residual heart damage. However, steroids are indicated in patients who develop congestive heart failure. Current understanding suggests unlikely benefit from digoxin, with the exception of associated arrhythmias. Occasionally, severe incompetence of aortic and/or mitral valves leads to refractory heart failure, which requires surgical implantation of a prosthetic valve.

### *Sydenham Chorea*

Because chorea often occurs as an isolated manifestation after the resolution of the acute phase of the disease, anti-inflammatory agents are usually not indicated. Sedatives may be helpful early in the course of chorea phenobarbital (16–32 mg every 6–8 hours PO) is the drug of choice. If phenobarbital is ineffective, then haloperidol (0.01–0.03 mg/kg/24 h divided bid PO) or chlorpromazine (0.5 mg/kg every 4–6 hours PO) should be initiated. Some patients may benefit from a few week course of corticosteroids.

Specific treatment for chorea is not available. Physical and mental stress should be minimized, and protective measures to prevent injury during severe episodes should be instituted. In very severe cases, steroids, phenobarbital, and valproic acid have been helpful.

### **Eradication of Streptococcal Infection**

#### *Antibiotic Therapy*

A full course of oral or intramuscular penicillin as given for GAS pharyngitis should be administered to all patients with ARF even if testing for GAS is negative. An oral cephalosporin is an acceptable alternative; macrolide antibiotics, such as erythromycin, clarithromycin, or azithromycin, should be limited to penicillin-allergic patients.

Once the diagnosis of ARF has been established and regardless of the throat culture results, or a single intramuscular injection of benzathine penicillin to ensure eradication of GAS from the upper respiratory tract. Long acting benzathine penicillin depending on age and weight of child, a single intramuscular injection of 0.6–1.2 million IU, 250–500 mg orally 2–3 times a day for 10 days or amoxicillin 50 mg/kg (maximum 1 g) once daily for 10 days. If penicillin-allergic, 10 days of erythromycin, azithromycin (5 days) or clindamycin is indicated. After this initial course of antibiotic therapy, long-term antibiotic prophylaxis should be instituted.

### **Primary Prevention**

Prophylaxis against recurrent ARF should be instituted immediately following acute therapy. The most effective prophylaxis consists of benzathine penicillin G intramuscular injections every 4 weeks; the injection can be painful and may lead to reactions. Alternative therapy consists of either oral penicillin V twice daily or oral sulfisoxazole once daily. Patients without rheumatic heart disease are at lower risk recurrence than are patients with

carditis or valvar disease. In pediatric ARF patients without carditis, prophylaxis should continue for at least 5 years or until age 21, whichever is longer.

Most acute pharyngitis is caused by virus and, less commonly, other bacteria. The epidemiologic peak of GAS pharyngitis and the risk for developing ARF are between 5 and 15 years of age. Protocols for testing for acute GAS pharyngitis in adults account for the lower GAS prevalence and risk for ARF beyond 15 years of age are not to be used in children.

Preferred regimens include oral penicillin V 2–3 times daily or a single daily dose of amoxicillin for 10 days. Parenteral benzathine penicillin is generally reserved for patients with poor compliance. Penicillin-allergic patients should receive a first-generation cephalosporin, clindamycin, or a macrolide. Macrolide resistance by GAS varies geographically. Testing for cure is not generally indicated.

Appropriate antibiotic therapy instituted before the 9th day of symptoms of acute GAS pharyngitis is highly effective in preventing first attacks of acute rheumatic fever. Long-term (possibly lifelong) prophylaxis is recommended for patients with residual rheumatic heart disease.

Antibiotic prophylaxis should continue in these patients until the patient reaches 21 years of age or until 5 years have elapsed since the last rheumatic fever attack, whichever is longer. The decision to discontinue prophylactic antibiotics should be made only after careful consideration of potential risks and benefits and of epidemiologic factors such as the risk for exposure to GAS infections.

The following preventive regimens are in use:

- *Penicillin G Benzathine*: 6,000,000 units for less than 27 kg, 1.2 million units for more than 27 kg intramuscularly every 4 weeks is the drug of choice.
- *Penicillin V*: 250 mg orally twice daily is much less effective than intramuscular Benzathine penicillin.
- *Sulfadiazine*: 500 mg for less than 27 kg, 1 g more than 27 kg once daily. This is recommended regimen for penicillin patients.

- *Erythromycin*: 250 mg orally twice a day may be given to the patients allergic to both penicillin and sulfonamides. Azithromycin or clarithromycin may also be used.

## Secondary Prevention

Secondary prevention is directed at preventing acute GAS pharyngitis in patients at substantial risk of recurrent ARF. The regimen of choice for secondary prevention is a single intramuscular injection of benzathine penicillin G (600,000 IU for children weighing <27 kg and 1.2 million IU for those weighing >27 kg) every 4 weeks. In certain high-risk patients, and in certain areas of the world where the incidence of rheumatic fever is particularly high, use of benzathine penicillin G every 3 weeks may be necessary because serum concentrations of penicillin may decrease to marginally effective levels after 3 weeks.

Secondary prevention requires continuous antibiotic prophylaxis, which should begin as soon as the diagnosis of ARF has been made and immediately after a full course of antibiotic therapy has been completed. Because patients who have had carditis with their initial episode of ARF are at higher risk for having carditis with recurrences and for sustaining additional cardiac damage, they should receive long-term antibiotic prophylaxis well into adulthood and perhaps for life.

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# Hurler Syndrome

## PRESENTING COMPLAINTS

A 9-year-old girl was brought with the complaints of:

- Delay in developmental milestones since birth
- Deafness since 6 years
- Behavioral problems since 4–5 years

## History of Presenting Complaints

A 9-year-old girl was brought by the parents with the history of behavioral problems to pediatric psychiatry outpatient department. The behavioral problems include both aggressive and depressive moods. She was fighting with her brothers in the house. Sometimes she was banging her own head to the table or wall. Child was admitted in the ward for the control of the behavioral problems.

### CASE AT A GLANCE

#### Basic Findings

Height	: 130 cm (40th centile)
Weight	: 36 kg (90th centile)
Temperature	: 37°C
Pulse rate	: 100 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 100/80 mm Hg

#### Positive Findings

##### History

- Mental retardation
- Deafness
- Consanguineous marriage
- Behavioral problems
- Delay in motor milestones

##### Examination

- Upward slanting of eyeball
- Short stature
- Short thick neck
- Hirsute features
- Hepatomegaly

##### Investigations

- Upward slanting of eyeball
- Urinary excretion of keratin and dermatan phosphate
- *X-ray of the hand*: Wide metacarpals
- *X-ray of the skull*: Long vertical diameter, shallow pituitary fossa, deep serration of the coronal suture

## Past History of the Patient

She was the elder sibling of the consanguineous marriage. Parents were cousins. She was born at term with the normal delivery. There was no history suggestive of the birth asphyxia. The newborn was breastfed soon after delivery. At the time of birth, the weight was 3.5 kg, the length was 45 cm, and head circumference was 35 cm.

The weaning of the child started at 4 months and the girl was eating the family foods by 18 months onwards. The child used to have feeding problems such as vomiting and sometimes choking. Motor development was slightly delayed. Speech development was impaired probably because of deafness. Child was mentally retarded and partially deaf. The child was immunized as per schedule.

## EXAMINATION

The girl was moderately built and nourished. She was plotted on the 90th centile for weight, i.e., 36 kg and 40th centile for the height, i.e., 130 cm. The girl had coarse and hirsute features. She was short and had thick neck. She was sitting quietly.

Child was afebrile. The pulse rate was 100 per minute and the respiratory rate was 26 per minute. The blood pressure recorded was 100/80 mm Hg.

There was no pallor, no lymphadenopathy, and no clubbing. She was partially deaf. Eye examination was normal. Per abdomen examination revealed the presence of hepatomegaly measuring about 4 cm below the costal margin. It was nontender and firm in consistency. Cardiovascular system revealed no murmurs. Respiratory system was normal. Skull and spine were normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 6,800 cells/cu mm
ESR	: 32 mm in the 1st hour
Absolute eosinophil count	: 426 cell/dL
Urine routine	: Normal
Urine	: Keratin level is increased, dermatan phosphate level also increased

X-ray of the hand : Showed wide metacarpal  
 X-ray of the skull : Showed long vertical diameter,  
 Shallow pituitary fossa, deep  
 serration of coronal suture

## DISCUSSION

Family history of the consanguineous marriage, mentally retarded child with behavioral problems and associated deafness give the clue to hereditary disease, Hurler's disease. Along with the physical examination findings such as short stature, thick neck, hirsute features and hepatomegaly, the diagnosis of the mucopolysaccharidosis is made. Urinary excretion of the keratin and dermatan phosphate and radiograph of hand revealing the wide metacarpal will consolidate the diagnosis.

Hurler's disease is a severe progressive disorder. This involves the multiple organs and tissues such as cornea, heart, brain, and skeletal leading to premature death. Usually before the age of 10 years.

The basic defect is the deficiency of alpha-L-iduronidase. This results in the accumulation of the dermatan sulfate and heparin sulfate in the tissues. These are also excreted in urine. Almost all the tissues in the body are involved. There will be progressive mental and physical deterioration.

In brain, the lipid storage occurs with the mucopolysaccharide accumulation. There is unusual hyalinization of collagen bundles. This leads to joint deformities and stiffness, thickened meninges, hydrocephalus, peripheral nerve compression, and tendency to develop hernia.

There will be narrowing of the coronary arteries, thickening of the cardiac valve and endocardium. Stiffening of the myocardium leads to congestive cardiac failure. Acute cardiomyopathy may be the feature of some infants. The constricted thorax contributes to the clinical deterioration of the patient.

### ESSENTIAL DIAGNOSTIC POINTS

- Autosomal recessive
- Mental retardation
- Hepatosplenomegaly
- Umbilical hernia
- Coarse facies
- Corneal clouding
- Dorsolumbar gibbus
- Severe heart disease
- Heparin sulfate and dermatan sulfate are found in urine

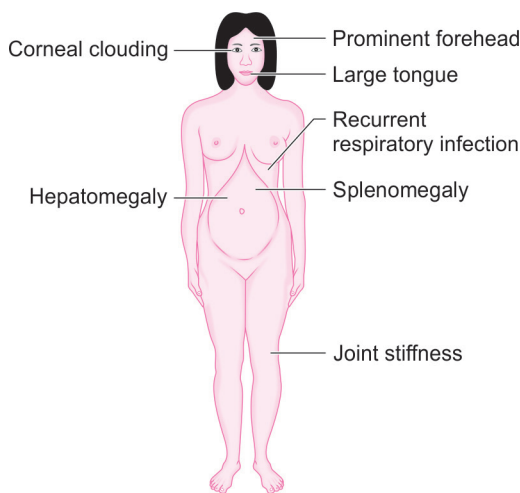
## CLINICAL FEATURES (FIG. 1)

The infant with Hurler's disease appear normal at birth. Hepatosplenomegaly, skeletal deformity, corneal clouding, coarse facial features, large tongue, prominent forehead, short stature, stiffness in the joint occur in between the ages of 6 and

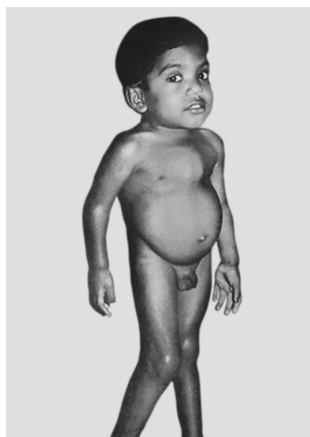
24 months. There will be delay in language development as a result of the chronic hearing loss and large tongue. There will be both conductive and sensorineural hearing loss.

The facial features appear progressively coarser. There will be frontal bossing, prominent sagittal, and metopic sutures. There is depressed nasal bridge. Nose is broad and flat. The child will deteriorate rapidly at second and 3rd year of life. These children become immobile. Joints become progressively stiff and contracted (**Fig. 2**).

Communicating hydrocephalus can occur as a result of progressive ventricular enlargement. Head will be large—dolichocephalic (**Fig. 3**). Recurrent respiratory tract infection, ear infection, noisy breathing, persistent nasal discharge are present. Clouding of the cornea (**Fig. 4**), umbilical, and inguinal hernias are common. Mental retardation is obvious. Glaucoma and retinal detachment are common.



**Fig. 1:** Clinical features.



**Fig. 2:** Hurler syndrome.





**Fig. 3:** Dolichocephalic.



**Fig. 4:** Corneal clouding.  
(For color version see Plate 8)

## DIAGNOSIS

The initial diagnostic test is the urinary excretion of glycosaminoglycans. Any individual who is suspected on clinical features, radiographic reports, urinary screening definitive diagnosis should be done by enzyme assay. Serum, leukocytes, or cultured fibroblasts are used as a tissue source for measuring lysosomal enzymes. Prenatal diagnosis is routinely carried out on cultured cells from the amniotic fluid or chorionic villus biopsy.

Radiograph of the patient in Hurler's disease reveals dysostosis multiplex. This includes dolichocephalic head and thickened calvarium. The medial third of the clavicle is thickened. There will be beak-like projection on the lower anterior margin. There will be premature closure of the lambdoid and sagittal sutures. There will be enlarged J-shaped sella, shallow orbits, abnormal spacing of teeth with the dentigerous cyst.

The diaphyses of the long bones are enlarged and irregular appearance of the metaphyses.

The pelvis is poorly formed with small femoral head. Coxa valga is present. The clavicles are short, thickened and irregular. The ribs are narrowed at the vertebral end and flat and broad at sternal end. The phalanges are short.

### GENERAL FEATURES

- Skeletal deformity
- Coarse facial features
- Glaucoma
- Hearing problem
- Retinal degeneration
- Kyphosis

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes:

- Hurler-Scheie syndrome
- Scheie syndrome
- Hunter syndrome
- Sanfilippo syndrome
- Morquio syndrome

## TREATMENT

There is no definitive treatment. The corrective factors are the missing lysosomal enzymes. Replacement of these enzymes by the administration of plasma or leukocytes are not satisfactory. Bone marrow transplantation has resulted in significant clinical improvement of the somatic disease and increased long-term survival. Improvement is seen with joint stiffness, facial appearance, hepatosplenomegaly, heart disease, and hearing loss. But skeletal or ocular anomalies are not corrected. Orthopedic correction includes femoral osteotomies, acetabular reconstruction, and posterior spinal fusion. The neurological outcomes are varied.

Supportive management with particular attention to respiratory, cardiac complications, hearing loss, carpal tunnel syndrome, spinal cord compression and hydrocephalus improves the quality of life. These patients require evaluation of their clinical status on regular basis.

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# Juvenile Rheumatoid Arthritis

## PRESENTING COMPLAINTS

A 6-year-old girl was brought with the complaints of:

- Pain in the finger since 1 week
- Swelling of the small joint since 1 week
- Fever since 3 days

## History of Presenting Complaints

A 6-year-old girl was brought to the outpatient department with history of pain in fingers of the hand and swelling of the small joints. Mother told that her daughter developed these complaints since 1 week. In the beginning she developed pain in the joints of the fingers of the hands. Pain became much severe restricting the movements. The presence of the swelling at the joint was also noted. It was associated with history of fever. Fever was of moderate to high degree continuous type. There was no history of rigors and chills.

### CASE AT A GLANCE

#### Basic Findings

Height	: 114 cm (50th centile)
Weight	: 18 kg (50th centile)
Temperature	: 38°C
Pulse rate	: 124 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 80/60 mm Hg

#### Positive Findings

##### History

- Joint pain
- Joint swelling
- Fever

##### Examination

- Febrile
- Toxic
- Lymphadenopathy
- Splenomegaly

##### Investigation

- Hb: 9 g/dL
- ESR: Raised
- X-ray of joint: Soft tissue swelling and increased joint space

## Past History of the Patient

She was the only sibling of nonconsanguineous marriage. She was born at term by normal vaginal delivery. There was no significant postnatal event. Her birth weight was 3 kg. She started taking breast milk on the 1st day itself. She was exclusively on breast milk for 4 months, weaning of the feeds started later with cereals, and she was on family food by 15 months. Her developmental milestones were normal. She had been completely immunized. Her performance at school was above average. There was no family history of similar complaints.

## EXAMINATION

The girl was moderately built and moderately nourished. She was looking toxic and she was crying in agony. She was not allowing anybody to touch her fingers. Her anthropometric measurements included, the height was 114 cm (50th centile), and the weight was 18 kg (50th centile). She was febrile, i.e., 38°C. The heart rate was 124 per minute, the respiratory rate was 26 per minute. The blood pressure recorded was 80/60 mm Hg.

She was pale. There was no cyanosis, no clubbing. There was cervical lymphadenopathy and there was no icterus. Per abdomen examination revealed presence of splenomegaly. Spleen was palpable about 3 cm below the costal margin. Respiratory cardiovascular system was normal.

## INVESTIGATION

Hemoglobin	: 9 g/dL
TLC	: 9,800 cells/cu mm
DLC	: $P_{72} L_{26} E_2 M_0$
ESR	: 56 mm in the 1st hour
Serum IgM	: Increased
X-ray of the joints	: Soft tissue swelling and increase in joint space

## DISCUSSION

A girl presented with history of pain in the finger of the hand and associated with the swelling in joint.

These symptoms along with the raised erythrocyte sedimentation rate (ESR) and radiographic finding help in diagnosis of juvenile rheumatoid arthritis (JRA).

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and one of the more common chronic illnesses of childhood. JIA represents a heterogeneous group of disorders all sharing the clinical manifestation of arthritis. The etiology and pathogenesis of JIA are largely unknown, and the genetic component is complex, making clear distinction among various subtypes difficult.

Juvenile rheumatoid arthritis is a clinical syndrome in which one or more joints show inflammatory changes lasting for more than 3 months. It may occur at any time after infancy. The peak age of the onset is children between 2.5 years. Girls are more prone than boys.

It is an autoimmune disease with major histocompatibility complex (MHC) associated with genetic predisposition. Environmental triggering factors include, e.g., infection with rubella virus, parvovirus 19, mycobacterium, trauma, psychological stress are linked to the onset of JRA.

There is nonspecific inflammation of the synovial membrane. Synovial tissue is edematous, hyperemic and infiltrated with lymphocytes and plasma cells. Joint spaces are filled with inflammatory fluid.

Complement activation and consumption probably play an important role in the inhibition and perpetuation of the inflammatory response. These are believed to secrete inflammatory cytokine. A number of autoantibodies, i.e., antinuclear antibodies and antismooth muscle antibodies are seen. The immunoglobulin M (IgM) rheumatoid factor is usually negative.

## ETIOLOGY

The etiology and pathogenesis of JIA are not completely understood though both immunogenetic susceptibility and an external trigger are considered necessary. JIA is a complex genetic trait in which multiple genes may affect disease susceptibility. There is evidence that the interleukin-6 (IL-6) gene, confers susceptibility to systemic JIA (sJIA), with increased transmission of the -174G allele of the IL-6 in patients older than 5 years. Possible nongenetic triggers include bacterial and viral infections, enhanced immune responses to bacterial or mycobacterial heat shock proteins, abnormal reproductive hormone levels, and joint trauma.

## PATHOGENESIS

The JIA is an autoimmune disease associated with alterations in both humoral and cell-mediated immunity. T-lymphocytes have a central role, releasing proinflammatory cytokines favoring a type 1 helper T-lymphocyte response. Studies of T-cell receptor expression confirm recruitment of T-lymphocytes specific for synovial nonself antigens. B-cell activation, immune complex formation, and complement activation also promote inflammation. Inheritance of specific cytokine alleles may predispose to upregulation of inflammatory networks, resulting in systemic disease or more severe articular disease.

Systemic JIA is characterized by dysregulation of the innate immune system with a lack of autoreactive T cells and autoantibodies. It is therefore may be more accurately classified as an autoinflammatory disorder.

A disease of persistent inflammation of the synovium, JIA has long been considered a manifestation of autoimmunity; however, intense investigation has failed to identify autoantibodies or target antigens. It is postulated that persistence of microbial antigens initiates synovial inflammation through the action of antibodies against microbial antigens that cross-react with self (molecular mimicry). Another line of investigation presents evidence that an infection promotes the presentation of self-human leukocyte antigen (HLA) peptides to T cells.

Evidence for an infectious initiation of synovial inflammation includes the persistent arthritis seen after a variety of infections, including rubella and parvovirus. The clinical features (abrupt onset, high-spiking fever, rash, hepatosplenomegaly, lymphadenopathy, and serositis) and a clustering of cases in the autumn also suggest infection as an inflammatory trigger. Further, polymerase chain reaction has allowed identification of microbes and their antigens in synovial tissue in some arthritides not previously thought to be due to infection.

The immunologic cascade involved in JIA appears to be initiated by presentation of antigen(s) to T-lymphocytes by antigen-presenting cells (macrophages, B-cells, dendritic cells, fibroblasts, and endothelial cells). Cytokines then trigger polyclonal T-cell expansion and production of a variety of additional inflammatory mediators including prostaglandins, complement proteins, kinins, proteases, matrix metalloproteases, and lysosomal enzymes. The result is migration of additional inflammatory cells into the synovial

tissue and fluid, increased vascular permeability, and damage to cartilage and bone.

The histology of the inflamed synovium in all categories of JIA is identical to that of adult rheumatoid arthritis, with characteristic lymphocytic and plasma cell infiltration, and later villous hypertrophy and hyperplasia of the synovial lining. This process is accompanied by prominent vascular endothelial cell hyperplasia and angiogenesis, resulting in the secretion of large amounts of protein-rich synovial fluid and the migration of neutrophils, lymphocytes, and macrophages into the joint. Synovial-fluid white cell counts usually range from 2000 to 30,000/mL. However, even counts exceeding 100,000/mL may be seen in patients with systemic JIA.

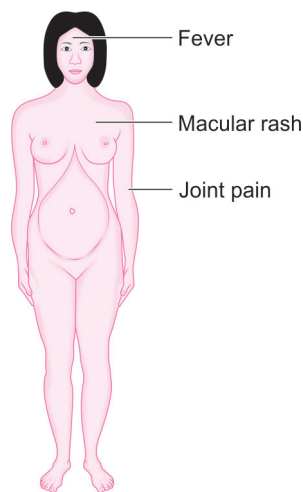
An exuberant inflammatory process leads to aggressive expansion of the synovium onto the articular cartilage, resulting in the so-called pannus formation. Lysosomal hydrolyses that break down proteoglycans and collagen facilitate invasion of the avascular cartilage by the pannus. Prolonged synovial inflammation causes irreparable damage to the cartilage, as well as erosion and destruction of subchondral bone. Formation of synovial-lined bony cysts can occur. New investigations have documented migration of activated macrophages into subchondral bone, with activation of osteoclasts, further contributing to chronic erosive changes.

Small areas of bone at the margins of articular cartilage (bare areas) are exposed directly to the inflamed synovium; erosions at these sites provide an early radiographic clue to bony destruction in inflammatory arthritis.

All these immunologic abnormalities cause inflammatory synovitis characterized pathologically by villous hypertrophy and hyperplasia with hyperemia and edema of the synovial tissue. Vascular endothelial hyperplasia is prominent and is characterized by infiltration of mononuclear and plasma cells with a predominance of T-lymphocytes. Advanced and uncontrolled disease leads to pannus formation and progressive erosion of articular cartilage and contiguous bone.

### CLINICAL FEATURES (FIG. 1)

Arthritis must be present to make a diagnosis of any JIA subtype. Arthritis is defined by intra-articular swelling or the presence of two or more of the following signs: limitation in range of motion, tenderness or pain on motion, and warmth. Initial symptoms may be subtle or acute and often



**Fig. 1:** Clinical features.

include morning stiffness with a limp or gelling after inactivity. Easy fatigability and poor sleep quality may be associated. Involved joints are often swollen, warm to touch, and painful on movement or palpation with reduced range of motion, but usually are not erythematous.

Arthritis in large joints, especially knees, initially accelerates linear growth and causes the affected limb to be longer, resulting in a discrepancy in limb lengths. Continued inflammation stimulates rapid and premature closure of the growth plate, resulting in shortened bones.

The patient's history and physical examination assume critical importance in establishing the diagnosis of JIA. A cardinal feature of inflammatory synovitis is morning stiffness of at least 30 minutes, with improvement over time or following movement and warming of the joint. Parents and other caregivers may observe changes in walking, running, climbing stairs, or eagerness to play. Children may need help with dressing, eating, bathing, toileting, and other activities that were previously performed independently. Enuresis may recur in a recently toilet-trained child, and developmental milestones may be lost. Children not old enough to describe stiffness or pain may be cranky or irritable in the morning or after a nap or have generally decreased activity.

On physical examination, all joints must be thoroughly assessed for swelling, tenderness, pain, motion, and bony enlargement. Muscles should be examined for strength and possible atrophy. In addition, extra-articular signs of juvenile arthritis, including abnormal pupils, rash, lymphadenopathy, organomegaly, and pericardial and

pleural rubs, should be sought. Occasionally, synovitis may be painless, but the diagnosis requires the physical finding of swelling resulting from inflammation. Loss or decreased motion with pain of the affected joints indicates chronicity of the joint inflammation and is indirect evidence of synovitis in those joints where swelling cannot be visualized (i.e., spine, hip, and shoulder).

### Oligoarticular Juvenile Idiopathic Arthritis

Oligoarticular type is most common type. It constitutes about 30–40% of patients. It is often asymmetrical. Children may develop leg length discrepancy, in which involved leg grows longer due to increased blood and growth factor.

Oligoarticular JIA, defined as arthritis in 4 or fewer joints over the first 6 months of symptoms. The ratio of males to females is 1:6.5; the usual age of onset is 1–3 years. Typically, the arthritis has an insidious onset and is minimally symptomatic. Many of these children will report no pain and come to medical attention after joint swelling is found incidentally. The knee is most frequently involved, followed by the ankle and then the small joints of the hand or the wrist; almost any joint, however, may be affected. Children with oligoarticular JIA are systemically well otherwise.

*Type I:* It is more common among female. Knees, ankles and elbows are commonly involved. There will be low grade fever and easy fatigueability. Iridocyclitis is observed in 25% patients. These require slit-lamp examination. Secondary glaucoma and cataract may develop. Antinuclear antibody (ANA) antibodies are positive. Rheumatoid factor is negative.

*Type II:* It is less common. Hip and girdle joints are involved. Sacroiliitis will develop. ANA antibodies and rheumatoid factors are negative. Family history of psoriasis, Reiter's disease and low back pain will be present.

Asymptomatic uveitis (inflammation of the uveal tract—iris, ciliary body, and choroid) develops in approximately 20% of children with oligoarticular JIA, and 80% of these children will have a positive antinuclear antibody test. Prompt diagnosis and treatment of uveitis are critical to prevent later cataracts and glaucoma and potential loss of vision. Consequently, ophthalmologic screening by slit-lamp examination every 3–4 months is essential for these high-risk children. Persistent or difficult-to-treat uveitis becomes the most prominent chronic feature in a subset of children with JIA.

Over time, approximately 80% of children with oligoarthritis will continue to have episodes of arthritis with 4 or fewer joints involved (persistent oligoarthritis), whereas 20% will have extension of synovitis into additional joints will be labeled as having extended oligoarthritis.

Enthesitis is most common in males, older 10 years of age. It is typically associated with lower extremity, large arthritis. The hallmark of this form is inflammation of tendinous insertion (enthesopathy), such as tibial tubercle or the heel. Carriage of HLA-B27 antigen is associated with increased risk of developing enthesitis-associated arthritis.

Psoriatic arthritis has typical psoriasis present and subtle changes such as nail pitting are present. They may also present with dactylitis or “sausage digit”, painful swelling of entire finger or toe.

The presence of a positive antinuclear antibody confers 20% increased risk for asymptomatic anterior uveitis, requiring periodic slit-lamp examination. ANA positivity may also be correlated with younger age at disease onset, female sex, asymmetric arthritis, and lower number of involved joints over time. Slit-lamp examination must performed at 3 months interval if ANA positive and at a 6-month interval if ANA negative for at least 4 years after onset of arthritis as this the period of highest risk.

Anemia is mild to moderate, normocytic or microcytic hypochromic type. Total leukocyte count is increased. Serum protein shows increase alpha 2 and gamma globulin fractions.

Lupus erythematosus may be demonstrated in few cases. IgM levels are elevated, radiograph of joints show soft tissue swelling and increased joint space. With destruction of articular cartilages, bone ends approximate and joint space is reduced.

Synovial fluid aspiration for microscopy and culture are indicated. Fluid predominantly shows polymorphonuclear response with low sugar and decreased complement.

### Polyarticular Juvenile Idiopathic Arthritis

Polyarticular JIA is defined as involvement of at least five joints during the first 6 months of illness, is found in approximately 25% of children with JIA. This group is further subclassified into the categories of rheumatoid factor (RF)-negative and RF-positive disease. Those children who are considered to be RF-positive must have this test confirmed with repeat testing at least 3 months from the initial test. Females predominate, with



2 peak ages of onset: 1–3 years, and again during early adolescence.

Both large and small joints may be affected; presentations vary from scattered joint involvement to symmetric synovitis of nearly all joints in the body. Involvement of the cervical spine, hips, shoulders, and temporomandibular joints (TMJ) are common finding. Micrognathia reflects chronic temporomandibular joint disease. Cervical spine involvement, manifesting as decreased neck extension, occurs with a risk of atlantoaxial subluxation and neurologic sequelae. Hip disease may be subtle, with findings of decreased or painful range of motion on examination. Flexion deformities of the knees, wrists and hips may develop. Proximal interphalangeal joints are involved.

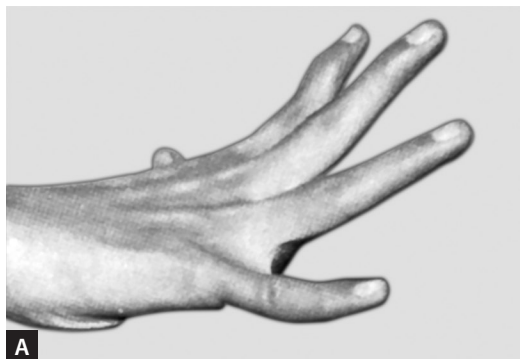
In most patients, the onset is insidious and accompanied by fatigue. Additionally, some patients have low grade fever, weight loss, hepatosplenomegaly, lymphadenopathy, pleuritic pericarditis, and pneumonitis. These patients are more likely to have elevated acute-phase reactants, including ESR, C-reactive protein (CRP), and platelet counts, and often may have mild anemia of chronic disease. White blood cell counts typically are normal.

The disease of children with a positive RF closely resembles adult rheumatoid arthritis, including occasional development of rheumatoid nodules, vasculitis, and Felty syndrome (splenomegaly and leukopenia). Antibodies to cyclic citrullinated peptide (anti-CCP) are found in many of the same patients, although they may develop earlier than the RF and may be a more sensitive marker of severe disease. Other serologic markers generally are negative; approximately 30% of patients with polyarticular JIA have positive ANA test results (**Figs. 2A and B**).

## Systemic Juvenile Idiopathic Arthritis

It is acute febrile, or systemic disease, i.e., Still's disease (sJIA). It accounts for 5–10%. The systemic manifestation includes fever, and rashes. Fever is intermittent. There is nonpruritic evanescent maculopapular rash in 90% of the patients. sJIA is characterized by arthritis, fever, rash, and prominent visceral involvement, including hepatosplenomegaly, lymphadenopathy, and serositis (pericarditis). The characteristic fever, defined as spiking temperatures to  $\leq 39^{\circ}\text{C}$  ( $102.2^{\circ}\text{F}$ ), occurs on a daily or twice-daily basis for at least 2 weeks, with a rapid return to normal or subnormal temperatures. The fever is often present in the evening and is frequently accompanied by a characteristic faint, erythematous, macular rash. The peak of the fever curve is often in the evening and may be accompanied by intense arthralgia and myalgia. When the temperature is normal, the child may feel quite well only to appear ill again when the fever spikes. Often the fever and other systemic features will precede the development of arthritis, so in general, systemic-onset JIA is a diagnosis of exclusion. Such patients must have an extensive or most reasonable evaluation to rule out other sources of fever, especially infections and malignancies.

Patients with systemic JIA may have a wide variety of systemic manifestations. Among them most common is a macular, evanescent, salmon-colored rash. It typically exhibits discrete borders with or without central clearing and is often best seen during the fever. The rash may be raised, is usually, nonpruritic, and is migratory, appearing anywhere, but most commonly over the trunk, thighs, and axillae. It may be induced by mild trauma (Koebner phenomenon). Other common systemic manifestations include pericarditis,



**Figs. 2A and B:** Juvenile polyarticular arthritis.

myocarditis, pleuritis, lymphadenopathy, hepatosplenomegaly, abdominal pain, fatigue, anorexia, weight loss, and rarely asymptomatic iritis. With time, a few or many inflamed joints will appear. They tend to be markedly swollen and more painful than the arthritis of other subgroups. Nighttime pain and awakening are not unusual, but they nonetheless should prompt investigation for underlying malignancy or infection. Neutrophilic leukocytosis (20,000–30,000 cells/cu mm) mild anemia, elevated sedimentation rate, elevated acute phase reactants are present. Antinuclear antibodies are present, but rheumatoid factors are negative).

The child with typical fever and rash but without arthritis may be treated empirically for probable systemic JIA after other diagnoses are exhaustively excluded. The diagnosis is not firm until synovitis appears and other potential causes of the child's symptoms have been duly considered. Many of these children will require bone marrow aspiration and/or lymph node biopsy to exclude malignant diseases. However, severe sequelaelargely may be avoided with prompt recognition and treatment with pulse intravenous (IV) methylprednisolone and further immunosuppression (e.g., with interleukin blockade with anakinra, or IV cyclosporine).

#### ESSENTIAL DIAGNOSTIC POINTS

- Nonarticular monoarticular or polyarticular arthropathy
- Proximal interphalangeal joints and large joints are involved
- Duration will last for more than 3 months
- Fever erythematous rashes, nodules leukocytosis.
- Iridocyclitis, pleuritis pericarditis
- Anemia, fatigue and growth failure

## DIAGNOSIS

As described for each category of JIA, there is no test or combination of tests that can differentiate JIA from other diseases. JIA remains a clinical diagnosis dependent on the finding of unexplained synovitis. The major role of laboratory tests is to exclude other potential diagnoses, particularly infection and/or malignancy, and to stratify patient's risk of developing disease sequelae. In cases of systemic arthritis, laboratory tests additionally help define severity of systemic inflammation.

## Radiographic Changes

The earliest changes are soft tissue swelling and periarticular osteopenia, although this latter

finding is only visible on plain radiographs when 50% of the bone mineral content has been lost because of inflammation. The intense inflammation of the tendon sheath, joint, and tendon attachments can stimulate periosteal new bone formation in the tubular bones of the phalanges, metacarpals and metatarsals, and occasionally long bones.

A characteristic radiographic finding in children with JIA involving a finger is widening of the midportion of a phalange from periosteal new bone formation. Plain radiographs are also useful for monitoring chronic joint changes and effectiveness of treatment, but ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) evaluations are more sensitive.

In young children, joint space widening can initially be seen because of increased intra-articular fluid or synovial hypertrophy. The hypervascularity of involved joints may stimulate adjacent growth plates and result in bony enlargement (e.g., knee or ankle) or epiphyseal advancement or closure (often seen in the wrist or hip).

Ultrasonography can identify synovial expansion, increased synovial fluid, and bony erosions. Ultrasound provides an inexpensive, easily available imaging technique that can assist clinicians in demonstrating subclinical synovitis and enthesitis as an adjunct to clinical examination and assessment, especially on the hips, shoulders, wrists, and ankles. MRI with IV gadolinium contrast provides the most complete imaging analysis, can assess the extent of synovitis and bone marrow edema, and can reliably show early erosive changes. CT is most useful for identifying bony abnormalities and erosions.

Joint space narrowing on plain radiographs and CT scanning is detectable only after a significant amount of cartilage has been destroyed. This detection typically takes longer. In children than in adults because of the relative thickness of cartilage during growth and may first become manifest in the TMJ. The TMJ is at particular risk for destruction because the epiphysis is as immediately adjacent to a thin fibrocartilage, which is not as robust as is true articular cartilage. When the epiphysis is destroyed, micrognathia due to lack of mandibular growth becomes evident. Coronal CT of the TMJ currently provides the best images for evaluation of joint damage in the TMJ. Whereas MRI with IV gadolinium can detect active synovitis.

Children with JIA involving the neck should be followed with flexion and extension lateral

radiographs of the cervical spine to assess the stability of C1 and C2 movement. Repeat films should be obtained before general anesthesia and if children are involved in gymnastics and contact sports.

Laboratory abnormalities of systemic JIA are often dramatic, including significant leukocytosis ( $>40,000$ ), thrombocytosis ( $>1$  million), and elevated inflammatory markers (e.g., CRP  $> 20$  mg/dL and ESR  $100$  mm/h). Elevated transaminases, anemia, and low serum albumin levels are found frequently, but urinalysis is normal.

During the acute phase of disease, some children become severely ill, with development of leukopenia, thrombocytopenia, profound anemia, and hypofibrinogenemia, and an acute decrease in the sedimentation rate. In addition, D-dimer and ferritin levels may rise dramatically, and prothrombin time and partial thromboplastin time become prolonged, consistent with disseminated intravascular coagulation. This crisis is called macrophage activation syndrome (MAS), and it appears to be related to hereditary lymphohistiocytosis. As it progresses, serum transaminases may abruptly increase to greater than  $1000$  U/L, the bone marrow may exhibit hemophagocytosis, and further sequelae of disseminated intravascular coagulation and cytokine storm may develop.

Elevated ANA titers are present in 40–85% of children with oligoarticular or polyarticular JIA, but are rare with sJIA. ANA seropositivity is associated with increased risk of chronic uveitis in JIA.

Children with sJIA usually have striking elevations in inflammatory markers and white blood cell and platelet counts. Hemoglobin levels are low, typically in the range of  $7$ – $10$  g/dL, with indices consistent with anemia of chronic disease. The ESR is usually high.

The main indication for joint aspiration and synovial analysis is to rule infection. A positive Gram stain and culture is definitive test for infection. A leukocyte count more than  $2000/\mu\text{L}$  suggests inflammation. A very low glucose concentration ( $<40$  mg/dL) or very leukocyte count  $>60,000/\mu\text{L}$  is suggestive bacterial arthritis.

### Laboratory Criteria

- Cytopenias
- Abnormal liver function tests
- Coagulopathy (hypofibrinogenemia)
- Decreased erythrocyte sedimentation rate
- Hypertriglyceridemia
- Hyponatremia

- Hypoalbuminemia
- Hyperferritinemia
- Elevated sCD25 and sCD 163

### Clinical Criteria

- Nonremitting fever
- Hepatomegaly
- Splenomegaly
- Lymphadenopathy
- Hemorrhages
- Central nervous system dysfunction (headache, seizures, lethargy, coma, disorientation)

### Histopathological Criteria

- Macrophage hemophagocytosis in the bone marrow aspirate
- Increased CD163 staining of the bone marrow.

#### GENERAL FEATURES

- Morning stiffness
- Fatigue
- Oligoarthritis
- Polyarthritis

#### LABORATORY SALIENT FINDINGS

- Rheumatoid factor is positive
- ANA is present in pauciarticular disease
- Joint fluid analysis
- Anemia—normocytic or microcytic hypochromic, leukocytosis
- Increased alpha 2 and gamma globulin in serum.
- IgM levels are elevated
- Radiograph of joint—increased joint space soft tissue swelling
- Synovial fluid aspiration for microscopy and culture

### DIFFERENTIAL DIAGNOSIS

- Systemic lupus erythematosus (SLE)
- Dermatomyositis
- Vasculitis syndrome
- Scleroderma
- Lyme disease
- Reactive arthritis
- Rheumatic fever

### COMPLICATIONS

- Chronic anterior uveitis
- Joint contractions
- Growth disturbances
- Amyloidosis

### TREATMENT

Treatment includes: (i) medical therapy, (ii) physiotherapy, and (iii) psychotherapy.

## Medical Therapy

The goals of treatment are to achieve disease remission, prevent or halt joint damage, and foster normal growth and development. All children with JIA need individualized treatment plans, and management is tailored according to disease subtype and severity, presence of poor prognostic indicators, and response to medications.

Early diagnosis of JIA is the cornerstone of most effective therapy. Goals of treatment are to minimize or resolve symptoms, prevent joint destruction, maintain normal growth and development, and achieve inactive disease. Inactive disease is defined as no joints with active arthritis; no systemic features such as fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no uveitis; normalization of inflammatory markers such as ESR or CRP; and normal physician's global evaluation.

## Medications

Timely use and correct choice of currently available medications to achieve sustained remission with as few side or adverse effects as possible remain the most challenging issues in the treatment of JIA.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are no longer the mainstay of treatment for arthritis, but they continue to be useful in the initial treatment for reduction of pain and as mild anti-inflammatory agents.

Intra-articular injections of triamcinolone acetonide or triamcinolone hexacetonide, in place of or in addition to systemic therapies, can be particularly effective in quickly suppressing inflammation in a limited number of joints. Depending on the age of the child and the number and location of joints to be injected, brief general anesthesia may be necessary for the injections. Repeat injections (up to 3 per joint) can be an important treatment strategy.

The administration (orally or intravenously) of systemic corticosteroids is mainly restricted to the management of the extra-articular features of systemic JIA (e.g., fever, anemia, pericarditis). A short course of low-dose prednisone may be considered for severe polyarthritis refractory to other therapies or while awaiting the effect of the recently initiated second-line or biologic therapy.

Corticosteroids are used for severe unremitting arthritis, systemic manifestation, i.e., pericarditis, myocarditis, vasculitis. Dose of prednisolone is 1–2/kg/mg/day; occasionally methylprednisolone (10–30 mg/kg) are necessary for severe unremitting arthritis, systemic manifestations such as

pericarditis, myocarditis, and vasculitis. Local steroid joint injection may be helpful. Triamcinolone hexacetonide is long acting steroid that can be used injection.

Methotrexate remains the most widely used initial disease-modifying therapy in JIA because of its efficacy at achieving disease control and acceptable adverse effects. Methotrexate can be given either orally or as a subcutaneous injection, with the latter having greater bioavailability at higher doses. For patients with polyarthritis or persistent or extended oligoarthritis, methotrexate should be started as early as possible. Folic or folinic acid supplementation may help prevent some or the adverse effects of methotrexate, in particular oral sores and ulcerations, nausea, and hematologic and liver enzyme abnormalities. Hydroxychloroquine is a useful adjunct and used along with methotrexate. Leflunomide may have efficacy and safety similar to those of methotrexate and is a reasonable alternative in a child with intolerance to methotrexate.

Nonsteroidal anti-inflammatory drugs alone rarely induce remission in children with polyarthritis or sJIA. Methotrexate is the oldest and least toxic of the DMARDs available for adjunctive therapy. It may take 6–12 weeks to see the effects of methotrexate. A low dose of methotrexate (5–10 mg/m<sup>2</sup>/week or up to 1 mg/kg/week as a single dose) are generally well tolerated. A complete blood count and liver function tests should be obtained every 2–3 months.

Nonsteroidal anti-inflammatory drugs:

*Naproxen*: 15–20 mg/kg/day. Maximum dose per day is 750 mg/day given twice daily.

*Ibuprofen*: 20–40/mg/day. Maximum dose per day is 2400 mg/day given four times daily.

*Aspirin*: 50–75 mg/kg/day. Maximum dose per day is 2000 mg/day given four times daily.

*Indomethacin*: 1–2.5 mg/kg/day. Maximum dose per day is 150 mg/day given three times daily.

*Diclofenac*: 2–3 mg/kg/day. Maximum dose per day is 150 mg/day given four times daily.

*Piroxicam*: 0.3–0.6 mg/kg/day. Maximum dose per day is 20 mg/day given once daily.

Failure of methotrexate monotherapy warrants the addition of a biologic DMARD.

**DMARDs** (Disease modifying antirheumatic drugs).

- Gold salts — 0.25 mg/kg/week increased gradually to 1 mg/kg/week
- d-penicillamine
- Hydroxychloroquine.

With the advent of newer DMARDs, the use of systemic corticosteroids can often be avoided or minimized. Systemic steroids are recommended only for management of severe systemic illness, for bridge therapy during the wait for therapeutic response to a DMARD, and for control of uveitis. Steroids impose risks of severe toxicities, including Cushing syndrome, growth retardation, and osteopenia, and they do not prevent joint destruction.

Intra-articular injections of glucocorticoids—triamcinolone are preferred therapy for children with oligoarthritis who do not respond to an initial trial of NSAIDs. Systemic glucocorticoids usually prednisolone 1–2 mg/kg/day, occasionally methylprednisolone (10–30 mg/kg) are necessary for severe unremitting arthritis, systemic manifestations such as pericarditis, myocarditis, vasculitis.

*Cytotoxic agents:* These are cyclophosphamide and azathioprine and very rarely required. Cyclosporine A is used in difficult cases.

Uveitis treatment is initiated with corticosteroid eye drops and dilating agents to prevent scarring between iris and lens. In patients who fail to topical treatment, methotrexate, cyclosporine, and/tumor necrosis inhibitor such as infliximab or adalimumab may be used.

#### *Newer modalities include biologic:*

During the past decade and a half, there has been quite a remarkable evolution in biologic therapy for adult and childhood arthritis. More focused anticytokine agents have been introduced and, to date, have been shown to be effective in better controlling arthritis and preventing joint damage, especially when administered earlier in the disease process.

These include anakinra (IL-1 receptor antagonist); canakinumab (monoclonal antibody to IL-1); tocilizumab (monoclonal antibody to IL-6 receptor); infliximab, golimumab and adalimumab [monoclonal antibodies to tumor necrosis factor (TNF)-alpha]; etanercept (recombinant soluble TNF receptor p75 fusion protein) and abatacept (inhibitor of T-cell activation).

Etanercept was the first anti-TNF therapy that was approved in the treatment of JIA; others with similar pharmacologic activity include infliximab, adalimumab, and golimumab. Co-stimulatory blocking agents (abatacept) provided another therapeutic option for those without good control with an anti-TNF agent. Anti-IL-1 (anakinra, rilonacept, canakinumab) and anti-L-6

(tocilizumab) agents have shown efficacy and tolerability for the treatment of systemic JIA.

All of the medications mentioned here (including NSAIDs) have potential side effects and require ongoing laboratory monitoring. Cytopenias and liver function abnormalities are seen most commonly for patients on methotrexate, complete blood count (CBC), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and creatinine are recommended after 1 month of treatment and then every 2–4 months. For NSAID use, the same monitoring (with a urinalysis) should be done 1 month after starting the medication and then every 4 months thereafter. Similar monitoring is recommended for most biologic agents.

Management of JIA must include periodic slit-lamp ophthalmologic examinations to monitor for asymptomatic uveitis. Optimal treatment of uveitis requires collaboration between the ophthalmologist and rheumatologist. Initial management of uveitis may include mydriatics and corticosteroids used topically, systemically, or through periorbital injection. DMARDs allow for a decrease in exposure to steroids, and methotrexate and antibodies to TNF-alpha (adalimumab and infliximab) are effective in treating severe uveitis.

Dietary evaluation and counseling to ensure appropriate calcium, vitamin D, protein, and caloric intake are important for children with JIA. Physical therapy and occupational therapy are invaluable adjuncts to any treatment program. A social worker and nurse clinician can be important resources for families, to recognize stresses imposed by a chronic illness, to identify appropriate community resources, and to aid compliance with the treatment protocol.

## **Physiotherapy**

Physical and occupational therapies are important components of the care and treatment of children with JIA. Goals include improving range of motion, strength, and function and preventing further deterioration. Because loss of age-appropriate developmental skills can occur, functional skills should be monitored by a therapist experienced in working with children with arthritis. Frequency of therapy visits varies considerably, but all therapy is based on a daily home program done by the child and parent. With severe ongoing disease, long-term cooperation with physical and occupational therapy can be difficult but is enhanced if the therapist tailors the home program



to take into account age, extent and severity of disease, school activities, sports, hobbies, and family dynamics. An active lifestyle is important for maintaining bone and joint health; low-impact exercises such as swimming are preferable when disease is active.

Night time splinting of the wrist, hand, knee, elbow, or ankle may decrease morning stiffness and help to prevent flexion contractures during active disease. Loss of extension can often be improved after corticosteroid injection followed by serial casting of a knee, ankle, wrist, finger, or elbow. Ice, heat ultrasound, or a combination of these modalities may help restore motion and decrease pain caused by muscle spasm. When a difference in leg-length is present, a shoe lift for the shorter limb will help to prevent contralateral knee or hip flexion contractures. Children with arthritis of the tarsal and metatarsal joints may ambulate more easily with shoe splints (soft orthotics).

## PROGNOSIS

Children with persistent oligoarthritis JIA have high rate of clinical remissions. Children with RF factor positive, disease are at higher risk for chronic erosive arthritis may continue adulthood. Prognosis in systemic disease is worse in patients

with persistent systemic disease after 6 months, thrombocytosis, and more extensive arthritis.

Tuberculosis screening should be done prior to initiation of any biologic treatment, and repeat surveillance should be performed annually while on anti-TNF agents.

Clinical follow-up of children with active JIA should occur every 1–3 months to allow for thorough evaluations and medication adjustments, with the goal of achieving disease remission. Meticulous surveillance for medication-related adverse effects is of prime importance, especially with the use of biologic agents. After inactive disease is achieved, medications are kept stable for 6 months to several years before they are gradually tapered and discontinued.

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# Congenital Hip Dislocation

## PRESENTING COMPLAINTS

A newborn baby girl was brought with the complaint of deformity in hip joint since birth.

## History of Presenting Complaints

A newborn baby girl was brought to orthopedic department as resident doctor of the pediatric department found some deformity in hip joint.

The baby was born by cesarean section at the term. The indication for the cesarean section was breech presentation. The baby cried immediately after the delivery. The cry of the baby was normal. The birth weight of the child was 3 kg. Activity of the child was normal. The pediatric resident who attended the delivery found hip of the child was abnormal. All movements at the hip joint were possible. Hence, the child was sent to orthopedic department to rule out congenital hip dislocation (CHD).

## EXAMINATION

The baby was lying on the bed. She was alert and active. She appeared normal. The anthropometric

measurements included, the length of the child was 51 cm (50th centile), the weight of the child was 3 kg (50th centile), and the head circumference was 35 cm. There was no pallor, no cyanosis, no lymphadenopathy, and no icterus. The pulse rate was 120 per minute and the respiratory rate was 22 per minute. The blood pressure recorded was 50/40 mm Hg.

Both the hips can be put through full range of movements. Conventional clinical examination of hip reveals no abnormality. Ortolani maneuver was positive. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 14 g/dL
TLC	: 8,600 cells/cu mm
DLC	: $P_{67} L_{26} E_4 M_3$
X-ray of the hip	: Normal

## DISCUSSION

The hip may be either dislocated or dislocatable at birth. The ligaments of the hips are unduly lax so that femoral head can be dislocated from acetabulum. The infant may lie on hip in dislocated position. Hip may be in reduced position but easily dislocatable. If the femoral head is allowed to remain out to acetabulum, shortening of ligaments makes reduction of the dislocation an increasing difficulty. If hip is allowed to remain dislocated until the child crawls and walks, the acetabulum fails to develop normally.

Developmental dysplasia of the hip (DDH) refers to a spectrum pathology in the development of the immature hip joint. This is also called as *congenital dislocation of the hip*. DDH more accurately described as the variable presentation of the disorder, encompassing mild dysplasia (as well as frank dislocation).

The etiology of DDH is multifactorial, but numerous predisposing factors have been identified. The classic risk factors for DDH include

### CASE AT A GLANCE

#### Basic Findings

Length	: 51 cm (50th centile)
Weight	: 3 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 120 per minute
Respiratory rate	: 22 per minute
Blood pressure	: 50/40 mm Hg

#### Positive Findings

##### History

- Breech presentation
- LSCS
- Deformities in the hip

##### Examination

- Active and normal child
- Ortolani test—positive

##### Investigation

- Normal

breech positioning, family history of DDH, first born, female sex, and a history of oligohydramnios. Breech positioning is considered a “packaging” issue (intrauterine crowding) predisposing to DDH. Torticollis, metatarsus adductus, and oligohydramnios are other packaging-related conditions strongly associated with DDH.

Developmental dysplasia of the hip as a condition in which the femoral head has an abnormal relationship to the acetabulum, specifically, the acetabulum does not completely cover the femoral head. It can result in hip joint instability. Dislocation is defined as complete displacement of a joint, with no contact between the original articular surfaces. Subluxation is defined as displacement of a joint with some contact remaining between the articular surfaces. Dysplasia refers to abnormal or deficient development of the acetabulum. A teratologic dislocation is a distinct condition that occurs before birth, is generally irreducible on physical examination, and causes the hip to be stiff. Teratologic dislocations often are associated with other syndromes and conditions, particularly arthrogryposis and myelodysplasia, and treatment depends on the underlying condition.

It commonly affects the left hip. At birth both acetabulum and femur are underdeveloped. Although the etiology remains unknown, the final common pathway in the development of DDH is increased laxity of the joint, which fails to maintain a stable femoroacetabular articulation. This increased laxity is probably the result of a combination of hormonal, mechanic and genetic factors.

Any condition that leads to a tighter intrauterine space and, consequently, less room for normal fetal motion may be associated with DDH. These conditions include oligohydramnios, large birth weight and first pregnancy.

Although most newborn screening studies suggest that some degree of hip instability can be detected in 1 in 100 to 1 in 250 babies, actual dislocated or dislocatable hips are much less common, being found in 1–1.5 of 1,000 live births.

## **PATHOANATOMY**

In DDH, several secondary anatomic changes can develop that can prevent reduction. Both the fatty tissue in the depths of the socket, known as the pulvinar, and the ligamentum teres can hypertrophy, blocking reduction of the femoral head. The transverse acetabular ligament usually

thickens as well, which effectively narrows the opening of the acetabulum. In addition, the shortened iliopsoas tendon becomes taut across the front of the hip, creating an hourglass shape to the hip capsule, which limits access to the acetabulum. Over time, the dislocated femoral head places pressure on the acetabular rim and labrum, causing the labrum to infold and become thick.

In more severe condition, femoral head is not in contact with acetabulum—dislocated hip. In dislocatable hip, femoral head is within the acetabulum but can be dislocated with provocative maneuvers.

Subluxative hip is one in which femoral head comes partially out of joint provocative maneuvers. Acetabular dysplasia is insufficient acetabular development.

## **CLASSIFICATION**

Developmental dysplasia of the hip is classified into two major groups—typical and teratologic.

The condition may be unilateral or bilateral. It is related to predisposition to joint laxity. This condition is predominant in female and in breech malposition of the fetus.

Congenital dislocation of the hip is classified into two major groups:

1. *Typical*: Occurs in neurologically normal infants.
2. *Teratologic*: Associated with underlying neuromuscular disorders such as myelodysplasia, arthrogryposis multiplex. The cause is multifactorial, physiological, mechanical, and postural.

## **CLINICAL FEATURES (FIG. 1)**

At birth, the hips are not dislocated except hip capsule and ligamentum teres are normal. If dislocation is allowed to occur acetabular dysplasia occurs. Maldirection, excessive femoral, and hip muscle contractures occur.

At birth, the appearance of infant is normal and the hips can be put through the full range of movements. Conventional clinical examination reveals no abnormality. Radiologically, the epiphyses of the femoral head do not appear until the 1st year of life. The acetabulum is largely cartilaginous so that even if the hip is dislocated, there is no obvious radiological abnormality. The relaxin is the hormone attributed to the condition (**Fig. 2**).

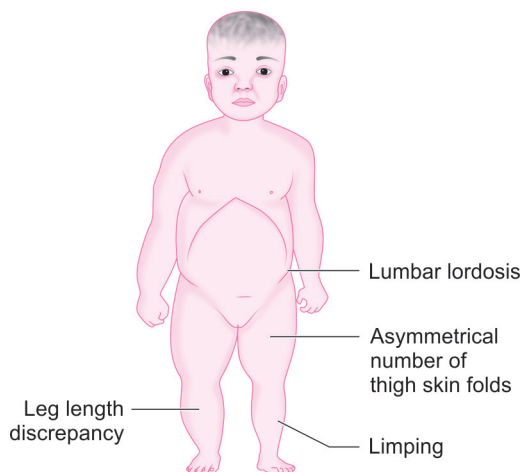


Fig. 1: Clinical features.



Fig. 2: Congenital dislocation of the hip.

## The Neonate

Developmental dysplasia of the hip in the neonate is asymptomatic and must be screened for by specific maneuvers. Physical examination must be carried out with the infant unclothed and placed supine in a warm, comfortable setting on a flat examination table.

**Ortolani test:** The demonstration includes eliciting the click from the hip. The hip is flexed at 90° and adducted. While the adduction is taking place, gentle pressure is exerted by examining hand in a proximal direction along axis of femoral shafts. As femoral head rolls over posterior hip of the acetabulum, if the hip is dislocatable. The femoral head slips out of acetabulum if the hip is dislocated. In unilateral congenital dislocation of hip, skin creases in the groin and buttocks are seen asymmetrically. The affected hip will have

full range of movements and telescoping may be demonstrated.

**Barlow's test:** It is the most important maneuver to examine hip dislocation of unstable hip. It is performed by stabilizing pelvis with one hand and then flexing and adducting the opposite hip and applying the posterior force. If the hip is dislocatable, it is usually readily felt. It gets relocated if the posterior force is released. The common concern is the presence of clicks in the infants. These will be secondary to breaking the surface tension across the hip joint, the snapping of the gluteal tendons, and femorotibial rotation, or patellofemoral rotation. In older children, limping, waddling, increased lumbar lordosis, toe walking, and leg length discrepancy indicate undiagnosed congenital dislocation of the hip.

**Hip click:** A hip click is the high-pitched sensation (or sound) felt at the very end of abduction during testing for DDH with Barlow and Ortolani maneuvers. Classically, a hip click is differentiated from a *hip clunk*, which is felt as the hip goes in and out of joint. Hip clicks usually originate in the ligamentum teres or occasionally in the fascia lata or psoas tendon and do not indicate a significant hip abnormality.

## The Infant

As the baby enters the 2nd and 3rd months of life, the soft tissues begin to tighten and the Ortolani and Barlow tests are no longer reliable. In this age group, the examiner must look for other specific physical findings, including limited hip abduction, apparent shortening of the thigh, proximal location of the greater trochanter, asymmetry of the gluteal or thigh folds, and positioning of the hip. Limitation of abduction is the most reliable sign of a dislocated hip in this age group.

Shortening of the thigh, the *Galeazzi sign*, is best appreciated by placing both hips in 90° of flexion and comparing the height of the knees, looking for asymmetry. Asymmetry of thigh and gluteal skin folds may be present in 10% of normal infants but suggests DDH. Another helpful test is the *Klisic test*, in which the examiner places the third finger over the greater trochanter and the index finger of the same hand on the anterior superior iliac spine. In a normal hip, an imaginary line drawn between the two fingers points to the umbilicus. In the dislocated hip, the trochanter is elevated, and the line projects halfway between the umbilicus and the pubis.

## The Walking Child

The walking child often presents to the physician after the family has noticed a limp, a waddling gait, or a leg-length discrepancy. The affected side appears shorter than the normal extremity, and the child toe-walks on the affected side. The Trendelenburg sign is positive in these children, and an abductor lurch is usually observed when the child walks. As in the younger child, there is limited hip abduction on the affected side and the knees are at different levels when the hips are flexed (the Galeazzi sign). Excessive lordosis, which develops secondary to altered hip mechanics, is common and is often the presenting complaint.

### GENERAL FEATURES

- Positive Barlow's test
- Positive Ortolani test
- Palpable click
- Hip adduction
- Waddling

### ESSENTIAL DIAGNOSTIC POINTS

- Positive Barlow's test
- Positive Ortolani test
- Palpable click
- Hip adduction
- Asymmetrical number of thigh skin folds
- Limping
- Waddling
- Increased lumbar lordosis
- Leg length discrepancy

## DIAGNOSIS

### Ultrasonography

The ultrasound examination can be used to monitor acetabular development, particularly of infants in Pavlik harness treatment; this method can minimize the number of radiographs taken and might allow the clinician to detect failure of treatment earlier.

In the Graf technique, the transducer is placed over the greater trochanter, which allows visualization of the ilium, the bony acetabulum, the labrum, and the femoral epiphysis. The angle formed by the line of the ilium and a line tangential to the bony roof of the acetabulum is termed the *alpha angle* and represents the depth of the acetabulum. Values  $>60^\circ$  are considered normal, and those  $<60^\circ$  imply acetabular dysplasia. The *beta angle* is formed by a line drawn tangential to the labrum and the line of the ilium; this represents the cartilaginous roof of the acetabulum.

A normal beta angle is  $<55^\circ$ ; as the femoral head subluxates, the beta angle increases.

Another useful test is to evaluate the position of the center of the head compared to the vertical line of the ilium. If the line of the ilium falls lateral to the center of the head, the epiphysis is considered reduced. If the line falls medial to the center of the head, the epiphysis is uncovered and is either subluxated or dislocated.

### Radiography

Radiographs are recommended for an infant once the proximal femoral epiphysis ossifies, usually by 4–6 months. In infants of this age, radiographs have proved to be more effective, less costly, and less operator dependent than an ultrasound examination. An anteroposterior (AP) view of the pelvis can be interpreted with the aid of several classic lines drawn on it.

The *Hilgenreiner line* is a horizontal line drawn through the top of both triradiate cartilages (the clear area in the depth of the acetabulum).

The *Perkins line* is a vertical line through the most lateral ossified margin of the roof of the acetabulum, drawn perpendicular to Hilgenreiner line. The ossific nucleus of the femoral head should be located in the medial lower quadrant of the intersection of these two lines.

The *Shenton line* is a curved line drawn from the medial aspect of the femoral neck to the lower border of the superior pubic ramus. In a child with normal hips, this line is a continuous contour. In a child with hip subluxation or dislocation, this line consists of two separate arcs and is described as “broken”.

The *acetabular index* is the angle formed between Hilgenreiner line and a line drawn from the depth of the acetabular socket to the most lateral ossified margin of the roof of the acetabulum. This angle measures the development of the osseous roof of the acetabulum. In the newborn, the acetabular index can be up to  $40^\circ$ ; by 4 months in the normal infant, it should be no more than  $30^\circ$ . In the older child, the *center-edge angle* is a useful measure of femoral head coverage. This angle is formed at the juncture of the Perkins line and a line connecting the lateral margin of the acetabulum to the center of the femoral head. In children 6–13 years old, an angle  $>19^\circ$  is normal, whereas in children 14 years and older, an angle  $>25^\circ$  is considered normal.

*Radiological evaluation:* Dynamic ultrasonography may be helpful in assessing acetabular development and hip stability. In lateral radiograph of the



pelvis, ossific nucleus of femoral head does not appear until 3–7 months of age. It may be further delayed in CHD.

#### LABORATORY SALIENT FINDINGS

- Dynamic ultrasonography to assess acetabular development and hip stability
- Arthrography
- CT or MRI

### DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes:

- Septic arthritis
- Osteomyelitis
- Perthes' diseases
- Tuberculosis

### COMPLICATIONS

- Avascular necrosis of femoral head
- Redislocation
- Residual subluxation
- Acetabular dysplasia
- Wound infection

### TREATMENT

The goals in the management of DDH are to obtain and maintain a concentric reduction of the femoral head within the acetabulum in order to provide the optimal environment for the normal development of both the femoral head and acetabulum.

Treatment is directed towards reduction of femoral head into acetabulum. Pavlik harness in the treatment of choice. This attempts to place the hip in human position by flexing them more than 90° (160–110°) and maintaining relatively full. But gentle abduction redirects femoral head to the acetabulum. Spontaneous relocation occurs within 3–4 weeks. If it does not occur surgical closed reduction is advised:

- Preliminary skin traction for 1–3 weeks to bring femoral head opposite to acetabulum
- Percutaneous adductor tenotomy
- Closed reduction
- Arthrography to assess correction of reduction

### Newborns and Infants younger than 6 Months

Newborns hips that are Barlow-positive (reduced but dislocatable) or Ortolani-positive (dislocated but reducible) should generally be treated with a Pavlik harness as soon as the diagnosis is made.

The management of newborns with dysplasia who are younger than 4 weeks of age is less clear. A significant proportion of these hips normalize within 3–4 weeks; consequently, many physicians prefer to reexamine these newborns after a few weeks before making treatment decisions.

The Pavlik harness remains the most commonly used device worldwide. By maintaining the Ortolani-positive hip in a Pavlik harness on a full-time basis for 6 weeks, hip instability resolves in 95% of cases. After 6 months of age, the failure rate for the Pavlik harness is >50% because it is difficult to maintain the increasingly active and crawling child in the harness. Frequent examinations and readjustments are necessary to ensure that the harness is fitting correctly. The anterior straps of the harness should be set to maintain the hips in flexion (usually 90–100°); excessive flexion is discouraged because of the risk of femoral nerve palsy. The posterior straps are designed to encourage abduction. These are generally set to allow adduction just to neutral, as forced abduction by the harness can lead to avascular necrosis of the femoral epiphysis.

### Children 6 Months to 2 Years of Age

The principal goals in the treatment of late-diagnosed dysplasia are to obtain and maintain reduction of the hip without damaging the femoral head. Closed reductions are performed in the operating room under general anesthesia. The hip is moved to determine the range of motion in which it remains reduced.

The reduction is maintained in a well-molded spica cast, with the “human position” of moderate flexion and abduction being the preferred position. After the procedure, single-cut CT or MRI may be used to confirm the reduction. 12 weeks after closed reduction, the plaster cast is removed; an abduction orthosis is often used at this point to encourage further remodeling of the acetabulum. Failure to obtain a stable hip with a closed reduction indicates the need for an open reduction. In patients younger than 2 years of age, a secondary acetabular or femoral procedure is rarely required. The potential for acetabular development after closed or open reduction is excellent and continues for 4–8 years after the procedure.

### Children older than 2 Years

Children 2–6 years of age with a hip dislocation usually require an open reduction. In this

age group, a concomitant femoral shortening osteotomy is often performed to reduce the pressure on the proximal femur and minimize the risk of osteonecrosis. Because the potential for acetabular development is markedly diminished in these older children, a pelvic osteotomy is usually performed in conjunction with the open reduction. Postoperatively, patients are immobilized in a spica cast for 6–12 weeks.

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## PRESENTING COMPLAINTS

A 7-year-old boy was brought with the complaint of hypopigmented patch since 2–3 months.

### History of the Presenting Complaints

A 7-year-old boy was brought by the mother to the pediatric outpatient with the history of hypopigmented patch over the buttocks and on inner side of the right thigh. Mother had noticed the development of the white patch since last 2–3 months. It was increasing in size. That worried her and made her to get the son to the hospital.

### Past History of the Patient

He was the first sibling of the nonconsanguineous marriage. He was born at full term with normal delivery. He cried immediately after the delivery. There was no significant postnatal event. He was discharged on 3rd day. He was on breast milk exclusively for 4 months. Weaning started at 4 months and completed at 18 months. There was no delay in developmental milestones.

#### CASE AT A GLANCE

##### Basic Findings

Height	: 122 cm (75th centile)
Weight	: 21 kg (50th centile)
Temperature	: 37.2°C
Pulse rate	: 120 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 100/70 mm Hg

##### Positive Findings

###### History

- White patches over the buttocks

###### Examination

- Hypopigmented patch
- Anesthetic patch

###### Investigation

- Buttock skin smear test

table. Anthropometric measurements included the height 122 cm (75th centile), the weight was 21 kg (50th centile).

He was afebrile, the pulse rate was 120 per minute and respiratory rate was 20 per minute. The blood pressure recorded was 100/70 mm Hg. There was no pallor, no lymphadenopathy and no edema.

There was hypopigmented patches present over the buttocks and on medial side of the thigh. There was loss of feeling to light touch, temperature and pain. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 10 g/dL
TLC	: 8,000 cells/cu mm
DLC	: P <sub>75</sub> L <sub>20</sub> E <sub>3</sub> M <sub>2</sub>
Platelet count	: 6,00,000 cells/cu mm
ESR	: 32 mm in the 1st hour
Urine routine	: NAD
Buttock skin smear test	: Lepa bacilli found

## DISCUSSION

Leprosy is a heterogeneous, chronic mycobacterial infection that primarily affects the upper airway, skin, and peripheral nerves. Disease manifestations are determined by the host's immunopathologic response to infection, resulting in a wide clinical spectrum.

## ETIOLOGY

*Mycobacterium leprae*, the etiologic agent of leprosy, is an obligate intracellular acid-fast gram-positive bacillus of the family Mycobacteriaceae measuring 1–8 micron in length.

Identification depends on criteria other than those used routinely for cultivable mycobacteria. Current criteria for *M. leprae* are the following: (1) it does not grow on routine laboratory media, (2) it infects the footpads of mice in a characteristic

## EXAMINATION

The boy was moderately built and nourished. The boy was sitting comfortably on the examination

manner, (3) acid fastness is abolished by exposure to pyridine, (4) the organism invades nerves of the host, (5) suspensions of dead bacilli produce a characteristic pattern of reactions when injected into the skin of patients (lepromin reaction) in accordance with the various clinical forms of leprosy, (6) it produces the species specific antigen phenolic glycolipid-1 (GLP-1), and (7) it exhibits species-specific DNA sequences.

The incubation period between natural infection and overt clinical disease in humans ranges from 3 months to 20 years, with a mean of 4 years for tuberculoid leprosy and 10 years for lepromatous leprosy. The infectiousness of patients with leprosy becomes negligible within 24 hours of the first administration of effective multidrug therapy.

## **PATHOGENESIS**

*M. leprae* causes disease by its ability to survive and multiply in macrophages. If macrophages of the host digest the bacilli early, disease is not detectable, or the patient has only minimal lesions. If the macrophages are totally incapable of destroying the organisms, widely disseminated lepromatous leprosy (LL) will follow. Apoptosis of host cells occurs but is not as important in the pathogenesis of leprosy as in some other mycobacterial infections. Survival of *M. leprae* in macrophages depends on the immune response of the patient.

The role of immunologic processes in damage to nerves in leprosy is poorly understood. Some observations suggest that antineural antibodies in the sera of many patients, especially those with lepromatous disease, are related to such damage. Tumor necrosis factor (TNF) is associated with macrophage infiltration of peripheral nerves in reversal reactions. Infected Schwann cells present antigens to T cells, making them targets for immune attack.

*M. leprae* is the only bacterium known to infect nerves. *M. leprae* has been shown to colonize the perineural space and gain entry into the endoneural space. The organism then binds to the laminin-2 glycoprotein present in the basal lamina of Schwann cells in peripheral nerves. It is then taken up inside the Schwann cell, where it replicates slowly intracellularly over several years.

Specific T cells recognize the mycobacterial antigens within the nerve and initiate a chronic inflammatory response. In addition to the direct nerve invasion by *M. leprae*, the immune response to infection also contributes to nerve damage.

Schwann cells express human leukocyte antigen class 2 molecules and play an important role in the immunologic reaction by presenting mycobacterial peptides to the human leukocyte antigen class 2—restricted CD4-positive T cells. This likely explains the nerve damage seen in paucibacillary disease and in reversal reactions. Swelling within the perineurium leads to ischemia, further nerve damage, and eventually to fibrosis and axonal death.

## **METHODS OF TRANSMISSION**

Infected patient is the only reservoir of the infection. Only those who are capable of discharging bacilli from their bodies transmit the infection (infectious or open cases). All active lepromatous or near lepromatous cases are open. During periods of reaction (acute exacerbation) closed or noninfectious cases may also become temporarily open or infectious.

The exact mechanism of transmission is not fully understood but is thought to occur primarily via the respiratory route. Up to  $10^7$  viable bacilli per day can be shed in the respiratory secretions of patients with multibacillary leprosy. Upper respiratory tract is considered the most probable site of entry of the organism into the human body. However, it is currently accepted that nasorespiratory transmission is most common. The nasal mucosa of lepromatous patients harbors massive numbers of *M. leprae*, known since Hansen's original discovery. *M. leprae* appears to bind to nasal mucosal cells by first binding fibronectin and then attaching to fibronectin receptors on mucosal cells. *M. leprae* organisms ejected during sneezing remain viable under ambient conditions for as long as 1 week, and disseminated leprosy develops in immunosuppressed mice after the inhalation of aerosol that contains *M. leprae*. Breast tissue and milk from lepromatous patients contain *M. leprae*, and infants may acquire infection from this source.

For many years, skin-to-skin contact between the patient and healthy subjects was considered the most important means of transmission, and this concept cannot be abandoned readily. Intact skin of heavily infected patients discharges small numbers of *M. leprae*, but ulcers in the skin may be a source of large numbers of bacilli. Thus, skin-to-skin contact and fomites containing *M. leprae* could be sources of infection.

Entry of the bacillus into the bodies of the infected persons produces widely different results because of differences in the sensitivity of the host.

On one end of the spectrum, in persons with high specific resistance, the bacilli are killed on entry into the body and no disease is produced. In persons with fairly high specific resistance, the bacilli can multiply only to a limited extent resulting in the production of mild, localized, self-limiting disease with scanty bacilli, viz., the tuberculoid type. In persons with little or no specific immunity, the bacilli can multiply rapidly, and spread widely in the body, resulting in generalized progressive disease with large number of bacilli, viz., the lepromatous type.

Type of disease (multibacillary) and proximity to contact cases are important determinants of human-to-human transmission. The relative risk for developing disease in household contacts is 8–10 for lepromatous disease and 2–4 for the tuberculoid form.

Discharge from ulcers in nose and skin are the usual sources of organism. Infants may acquire bacilli through breast milk. Discharges from the neuropathic ulcers in feet and hands do not contain bacilli.

### CLINICAL FEATURES (FIG. 1)

The disease is classified as lepromatous, borderline, indeterminate, maculoanesthetic, tuberculoid and polyneuritic. While lepromatous and tuberculoid represent the LL and tuberculoid tuberculoid (TT) types of immunological classification; maculoanesthetic group may comprise of the borderline tuberculoid (BT) and TT variants. Borderline group represents BT, borderline borderline (BB) and borderline lepromatous (BL) variants.

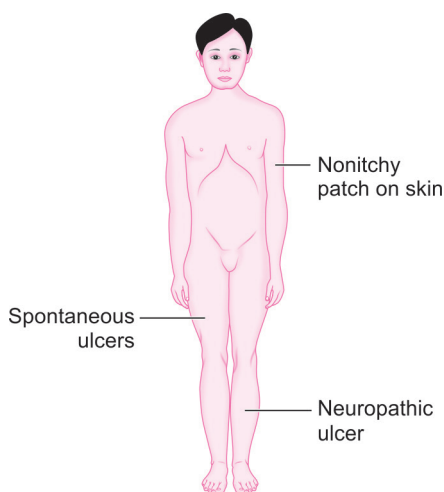


Fig. 1: Clinical features.

Classic manifestations of leprosy include hypopigmented, erythematous, or infiltrative skin lesions with or without neurologic symptoms such as hypoesthesia or anesthesia, weakness, autonomic dysfunction, and peripheral nerve thickening.

The period from infection to clinical disease varies (usually 2–5 years but up to 15 years reported), and no prodromal manifestations are well established. After an incubation period, lesions of varying description appear. The nature of the lesions depends on the immune response of the patient to *M. leprae*. Classification is important because it aids in establishing the treatment program and prognosis of the patient.

The cardinal signs of leprosy are hypoesthetic lesions of the skin, enlarged peripheral nerve or nerves, and AFB in skin smears. In the absence of another clear explanation, any one of these signs strongly suggests leprosy.

Virtually all patients with leprosy have peripheral neuropathy if cutaneous sensory changes are included, and approximately 25% have significant deformity, depending on the intensity of leprosy case finding and the inherent delays in detection. In experimental studies, the pathogenesis of peripheral neuritis in leprosy involves uptake of bacilli by the endothelial cells of epineural and perineural blood vessels and lymphatics. Surface proteins of *M. leprae* may bind the bacillus to Schwann cells via laminin.

Ocular complications in leprosy are well known. All patients with leprosy should be evaluated by an ophthalmologist at diagnosis and periodically thereafter, especially during any reactionary episodes.

### Indeterminate Leprosy

An indeterminate lesion is the first manifestation of leprosy in most patients, and may heal spontaneously, remain unchanged for months or years, or gradually progress toward TT or LL disease. Patients with indeterminate leprosy have a single or a few macules in the skin. The macule is poorly defined and mildly hypopigmented in deeper pigmented skin and slightly erythematous in lighter skin. Skin texture, sensation, and sweating within early macules are normal or only slightly altered. Peripheral nerves are not affected, and skin smears from lesions rarely contain bacilli.

### Tuberculoid Leprosy

Patients with TT have a single or several asymmetrically distributed hypopigmented skin lesions.



Tuberculoid lesions arise *de novo* or evolve from indeterminate macules. The lesion may be macular or infiltrated, but the borders are always sharply demarcated from the surrounding normal skin and are frequently finely papulated. Lesions range from less than 1 cm to those that cover entire regions such as the thigh or buttock. Many TT lesions heal spontaneously. In large, active lesions, the centers are often healed and repigmented, although somewhat atrophic.

In TT lesions, there is sensory loss with impaired sweating and eventually loss of hair. On the face, because of its rich innervation, the detection of hypoesthesia in early lesions requires discriminating tests. Conversely; clinicians may mistakenly diagnose leprosy in areas of the body that normally have reduced sensory acuity (e.g., over the elbows or knees).

Involvement of peripheral nerves commonly develops in TT leprosy and cutaneous nerves can often be palpated adjacent to or within lesions. The regional nerve trunks most commonly enlarged are the ulnar nerve from the olecranon groove to midarm, the lateral popliteal nerve just distal to the head of the fibula, and the posterior tibial nerve in the medial aspect of the ankle. Enlarged or tender nerves anywhere should alert the clinician to the possibility of leprosy. Any readily palpable cutaneous nerve is probably enlarged, but evaluating the size of nerve trunks requires experience because of the wide range in normal size.

## Borderline Leprosy

Borderline leprosy, sometimes called dimorphous or intermediate leprosy, has features of both the LL and the TT forms and represents a continuous spectrum of disease ranging from near-tuberculoid to near-lepromatous. It is an unstable form of leprosy and may evolve gradually toward TT leprosy by undergoing reversal reactions. LL leprosy describes the three major subgroups of borderline leprosy: BT, BB, and BL.

In BT leprosy, the number of lesions is usually greater than in TT leprosy, and the borders of each lesion, macule, or plaque are defined less sharply than in TT leprosy. There may be central clearing within lesions, small satellite lesions may develop around larger macules or plaques. BL leprosy often presents with widespread nodular infiltrations or plaques of varying size.

Damage to nerves and the resulting deformity develop early and are often widespread. Pain in nerves or neuropathic changes (e.g., sensory changes that lead to damaged hands or feet or

muscular weakness such as foot drop) frequently bring the patient to the physician. Severe damage to nerves is infrequent in early childhood but can be disastrous. Prevention of this complication is an important goal of leprosy detection programs and to treatment of every leprosy patient.

## Lepromatous Leprosy

In LL leprosy, the bacilli multiply freely and the disease disseminates widely, often before striking cutaneous manifestations develop, in contrast to the strict localization of lesions in TT leprosy. LL leprosy may evolve from indeterminate or BB leprosy or may be the first recognizable form.

In its earliest form, LL leprosy manifests as “juvenile leprosy,” a clinical entity delineated from observations on large numbers of children in homes for children of patients with leprosy in India. This form, also called prelepromatous leprosy, is difficult to detect and frequently goes unrecognized until a more advanced stage develops. Skin texture may be altered slightly, but the vague macules with indistinct borders are detected only under appropriate lighting, preferably daylight. There are no changes in sensation or sweating in the macules, and frequently acid-fast bacilli (AFB) are not detectable in smears from skin. Histopathologic sections may reveal a few bacilli to confirm the diagnosis. If leprosy is suspected, the patient should be monitored until an explanation for the mild skin changes is found. If leprosy is present but not detected and treated, advanced forms of LL leprosy will develop in many of these patients.

The hypopigmented or slightly erythematous macules of early LL leprosy, like those of juvenile leprosy, are missed easily because they are vague and have slight, if any, sensory changes. These macules are usually small but gradually may coalesce and cover large areas of skin, even nearly the entire body. A clinical diagnosis then is often missed, and over the course of a few years, advanced LL leprosy develops. If skin smears or biopsy specimens are taken in the macular stage, diagnosis is almost assured. If the disease is not diagnosed and treated in the macular stage, infiltration of the skin will increase gradually, and nodules may develop. The skin is infiltrated most heavily in the cooler portions of the body, notably the ears (pinnae) and face. By this time, nerves are usually enlarged, with early signs of sensory loss in the hands and feet. Eyebrows are thinned and eventually lost, beginning at the lateral edges. These advanced changes of LL leprosy are not

common findings in young children but are well known.

## Neuritic Leprosy

Rarely, leprosy involves one or more major nerve trunks unaccompanied by cutaneous lesions. These patients have anesthesia, paresis, or wasting of muscles in the affected area, nerve trunks are frequently painful, enlarged, and tender. Leprosy must be suspected in patients with any peripheral neuritis that has these features. Chronic neuritis with pain, enlargement, and tenderness of peripheral nerves often persists for years after the patient has completed chemotherapy for leprosy. Large leprotic nerve abscesses are rare but are exquisitely painful and may require surgical intervention for drainage. However, most clinicians prefer to treat such lesions with corticosteroids.

### GENERAL FEATURES

- Loss of feeling to touch, temperature and pain
- Loss of sensation
- Numbness
- Pins and needles

## Skin Involvement

Examination of the skin should ideally be performed in natural sunlight and be tested for hypoesthesia to light touch, pin prick, temperature, and anhidrosis. The most common skin lesions are macules or plaques. Diffuse infiltrative lesions and subcutaneous nodules are less common. Initial lesions are insidious hypopigmented macules, although they may appear erythematous on pale skin.

Cutaneous lesions (**Fig. 2**) range from apparently innocuous looking and probably self-healing solitary lesion to extensive involvement

of skin and mucous membranes with lesions of divergent nature. Skin is thick, red and shiny, especially on the face and hands.

Lesions may involve any area of the body, are more pronounced in cooler areas (for example the earlobes and nose), and occur less frequently on the scalp, axillae, or perineum. Approximately 70% of skin lesions have reduced sensation; the degree of hypoesthesia depends on the location and size of the lesion. Patients with tuberculous leprosy generally have 1–3 well-demarcated macules or plaques with elevated borders and reduced or absent sensation. In the lepromatous form, multiple lesions are present but are not all hypoesthetic or anesthetic.

## Nerve Involvement

The skin lesions overlying a nerve trunk distribution predict the involvement of nerves in the vicinity. Peripheral nerves are most commonly affected early in the disease course and should be palpated for thickness and tenderness and evaluated for both motor and sensory function (particularly temperature and light touch).

The posterior tibial nerve (medial malleolus) is the most common nerve affected, followed by the ulnar (elbow), median (wrist). Lateral popliteal (fibular neck), and facial nerves. A nerve biopsy (usually of the sural nerve) is required to demonstrate granulomatous histopathology, thereby confirming the diagnosis.

## Reactions

The course of leprosy, treated or untreated, is often interrupted by acute immunologically based episodes called reactions, which fall into two general categories: reversal reactions (or type 1) and erythema nodosum leprosum (ENL) or type 2 reactions.

## Reversal Reactions

Patients may also present with leprosy reactions. Leprosy reactions are acute clinical exacerbations reflecting disturbances of the immunologic balance to *M. leprae* infection occurring in 30–50% of all leprosy patients. These sudden changes occur most commonly during the initial years after infection and in patients with borderline and multibacillary leprosy, but can occur before, during, or after completion of treatment. Three types of leprosy reactions have been described and require immediate treatment so as to prevent complications.



**Fig. 2:** Cutaneous lesions  
(For color version see Plate 8)

*Type 1 reactions* (also known as reversal reactions) occur in one-third of patients with borderline disease and are caused by a spontaneous increase in T cell-mediated reactivity to mycobacterial antigens. Reversal reactions are characterized by acute edema and increased erythema, warmth, and painful inflammation of preexisting cutaneous plaques or nodules with acute swelling and tenderness of peripheral nerves that can quickly progress to cause nerve abscesses and necrosis. There may be a peripheral lymphocytosis and an increased cytokine response, but systemic symptoms are uncommon. Rapid and sustained reversal of the inflammatory process using corticosteroids is essential to prevent continued nerve damage.

Patients who are lepromin positive and have immunoglobulin M (IgM) antibodies to phenolic glycolipid-I (PGL-I) are most at risk for reversal reactions. Proliferation of sensitized T lymphocytes initiates reversal reactions, releasing lymphokines that amplify the inflammatory response, calling in and activating macrophages. Immunohistopathologic evidence has shown that effective chemotherapy for both paucibacillary and multibacillary patients may activate cell-mediated immunity and provoke clinical or subclinical reversal reactions. Differentiating reversal reactions from relapsing lesions is frequently difficult and requires careful correlation of clinical and histopathologic findings.

*Type 2 reactions* [erythema nodosum leprosum (ENL)] occur in borderline lepromatous and lepromatous forms, as these patients have the highest levels of *M. leprae* antigens and antibodies, most commonly in the first 2 years after starting chemotherapy. ENL is distinguished from reversal reactions by the development of new painful, erythematous subcutaneous nodules with an accompanying systemic inflammatory response. ENL is accompanied by high circulating concentrations of TNF-alpha. Patients develop high fever and signs of systemic toxicity, and in severe cases, ENL can be life-threatening, presenting with features similar to septic shock.

Patients present with either a single, acute episode, a relapsing form comprised of multiple acute episodes, or chronic, continuous form. Deposition of extravascular immune complexes leads to neutrophil infiltration and activation of complement in the skin and other organs. Tender, erythematous dermal papules or nodules (resembling erythema nodosum) occur in clusters, typically on extensor surfaces of the lower

extremities and face. Immune complex deposition also contributes to migrating polyarthralgias, painful swelling of lymph nodes and spleen, iridocyclitis, vasculitis, orchitis, and rarely nephritis.

*Type 3 reaction* Lucio's phenomenon (erythema necroticans) is an uncommon but potentially fatal reaction distinct from type 1 or 2 reactions that occurs in patients with untreated lepromatous leprosy. It is a necrotizing vasculitis caused by *M. leprae* directly invading the endothelium. Clinically, patients develop violaceous or hemorrhagic plaques, followed by ulcerations in the absence of systemic complaints. Secondary bacterial infections are common.

## DIAGNOSIS

A case of leprosy is defined as a person having one/more of the following features, and who has yet to complete a full course of treatment.

- Hypopigmented or reddish skin lesions with definite loss of sensation.
- Involvement of peripheral nerves, demonstrated by definite thickening with loss of sensation.
- Skin smear positive for acid-fast bacilli.

The disease should not be diagnosed if only nerve thickening is present, without any accompanying symptoms or signs. Diagnostic evaluation includes physical examination plus examination of skin smears. The examination should include evaluation of skin lesions, palpation of peripheral nerves such as the ulnar at the elbows, median and superficial cutaneous at the wrists, greater auricular in the neck and the common peroneal at the popliteal fossa, for enlargement and/or tenderness together with sensory (skin lesions and distal extremities) and motor evaluation.

### ESSENTIAL DIAGNOSTIC POINTS

- Hypopigmented or reddish skin lesions
- Definite loss of sensation
- Involvement of peripheral nerves
- Definite thickening with loss of sensation
- Skin smear positive for acid-fast bacilli

## Bacteriological Examination

If no definite patches of thickened skin are visible, smear should be taken from the ear lobes and buttocks. The small material thus obtained should be uniformly spread on clean glass slide, dried over flame, stained with Ziehl-Neelsen method, and examined under the microscope. At least 100 fields should be examined before recording a negative result.

## LABORATORY SALIENT FINDINGS

- *Skin smear*: Earlobes, buttocks
- Stained with Ziehl-Neelsen method
- Lepromin test
- Tests for humeral response
- Serology

Obtaining and examining smears for AFB is an important diagnostic procedure and should be controlled carefully by experienced laboratories. Briefly, smears are made from the edge of discrete macules or plaques, nodules, ear lobes, and nasal mucosa. Skin smears are made by squeezing and holding a fold of skin between the thumb and forefinger to avoid getting blood in the smear, and by making a short, shallow slit in the skin with a sterile razor blade or scalpel. The instrument is then turned at a right angle to the slit, and the edges of the incision scraped. The cells and fluid thus obtained are spread on a slide, heat-fixed, and stained by the Ziehl-Neelsen method. Evaluation of smears should not be done by researchers unfamiliar with their interpretation. An occasional AFB may be, for example, a contaminant in the staining reagents, although with appropriate quality controls, such false positives can be minimized.

**Lepromin test:** The lepromin test is carried out by injecting 0.1 mL of Mitsuda lepromin intradermally into the forearm and noting the reaction later at 21 days. It is of little use in diagnosis, though it is of value in classification and of prognosis. The test is graded as follows:

As a routine the reaction is read at 48 hours and at 21 days. Two types of positive reactions have been described.

**Early reaction:** It is also known as Fernandez reaction. As inflammatory reaction, i.e., response develops within 24–48 hours and this tends to disappear after 3–44 days. It is evidenced by redness and induration at the site of inoculation. If the diameter of the red area is more than 10 mm at the end of 48 hours, the test is considered as positive.

The early reaction indicates whether or not a person has been previously sensitized by exposure and infection by leprosy bacilli.

Negative	Nothing to see or feel
±	Papule 3 mm in diameter
+	Erythematous papule 4–7 mm diameter, no ulcer
++	Erythematous papule 7–10 mm diameter, no ulcer
+++	>10 mm erythematous nodule or less with ulceration

BCG vaccination is capable of converting lepra reaction from negative to positive in large number of patients.

It has been generally accepted as a useful tool in evaluating the immune status—CMI. It is of value in confirming the results of classification of cases of leprosy on clinical and bacteriological grounds. It helps in classification of the type of the disease.

It is useful in estimating the prognosis in case of leprosy of all types. It is strongly positive in typical tuberculoid cases. Positivity getting weaker through the spectrum of lepromatous end. Typical lepromatous patient being lepromin negative indicating failure of CMI.

## Tests for Humeral Response

**Fluorescent leprosy antibody absorption (FLA-ABS) test:** It is used for identification of subclinical infection. It is 92.3% sensitive, 100% specific in detecting *M. leprae*.

**Monoclonal antibodies:** These antibodies recognize specific and nonspecific epitopes of *M. leprae* antigens. If antibodies against specific antigen are found, they will become reagents of choice for identifying *M. leprae*. A serum antibody competition test (SACT) is based on this approach has been found to be quite sensitive for detection of *M. leprae* antibody. An ELISA based on a particular phenolic glycolipid, derived from *M. leprae* is also in use.

To confirm the diagnosis, a full-thickness skin biopsy should be taken from the most active skin lesion, entirely within the lesion and including the active margin. *M. leprae* is best identified in tissue using the Fite-Faraco stain. Lesions from patients with the lepromatous form reveal numerous acid-fast bacilli in clumps (globi), whereas patients with the tuberculoid form of the disease rarely have mycobacteria identified but demonstrate well-formed noncaseating granulomas and nerve involvement.

Biopsy specimens from well-defined lesions of leprosy should be taken from the active border and fixed in buffered 10% formalin or other suitable fixative, unless molecular studies are requested, in which case formalin should be avoided. The Fite-Faraco staining method is used because the Ziehl-Neelsen stain does not demonstrate *M. leprae* optimally in tissue sections. A histopathologic diagnosis of leprosy must not be made unless the evidence is convincing. DNA probes specific for *M. leprae* are available

and are useful in identifying leprosy bacilli in tissue or nasal secretions. Specimens for DNA evaluation or polymerase chain reaction (PCR) amplification should be preserved in 70% ethyl alcohol.

The presence of neural inflammation differentiates leprosy from other granulomatous disorders. Hematoxylin and eosin staining and immunohistochemistry may also contribute to the diagnosis. Mycobacterial culture of lesions is performed to exclude *M. tuberculosis* and non-tuberculous cutaneous infections. Antibodies to *M. leprae* are present in 90% of patients with untreated lepromatous disease, 40–50% with paucibacillary disease, and 1–5% of healthy controls. Serologic testing is insensitive, however, and is not used for diagnosis.

## DIFFERENTIAL DIAGNOSIS

Vitiligo, nutritional dyschromia especially of face, tinea versicolor, nevus anemicus (hypopigmented birth marks), hypopigmented scars left by pyogenic infections, etc., are considered in differential diagnosis of macular patches.

## TREATMENT

Once a diagnosis of leprosy is established, chemotherapy must be initiated. Because of drug-resistant *M. leprae*, combined multiple-drug treatment (MDT) regimens, such as WHO-MDT, are mandatory for the treatment of all forms of leprosy. Currently, drugs used in WHO-MDT and US-HT are a combination of rifampicin, clofazimine, and dapsone for multibacillary leprosy, and rifampicin and dapsone for paucibacillary leprosy. Rifampicin, the most important antileprosy drug, is used in both types of leprosy.

Appropriate measures are also begun for preventing or correcting deformity in patients with neuropathic changes. Neuropathic changes involve primarily nerves and other structures in the cooler parts of the body and are most profound in the eyes, face, hands, and feet. Damage to the hand, for example, is related to loss of normal autonomic, sensory, and motor function. Early appropriate surgical intervention can often restore motor function, and physiotherapy will maintain useful hands.

Patients of leprosy are classified into three groups based on clinical assumption: (i) paucibacillary single lesion (one skin lesion); (ii) paucibacillary leprosy (2–5 skin lesions); and (iii) multibacillary leprosy (>5 skin lesions). The primary goal of treatment is early antimicrobial

therapy to prevent permanent neuropathy. Effective treatment of leprosy requires MDT with dapsone, clofazimine, and rifampicin.

Combination therapy is employed to prevent antimicrobial resistance. Before starting combination MDT, patients should be tested for glucose-6-phosphate dehydrogenase deficiency, have a baseline complete blood cell count and liver function testing, and be evaluated for evidence of concomitant tuberculosis infection. The latter is imperative so as to avoid giving rifampicin monotherapy to someone with active tuberculosis.

Darkening of the skin is a common adverse reaction to clofazimine; this generally resolves 6–12 months after completing therapy. Bone marrow suppression and hepatotoxicity have been reported and should be monitored every 3 months during therapy. Yearly, a screening urinalysis should be performed.

Minocycline, clarithromycin, rifapentine, diarylquinoline, and some fluoroquinolones (ofloxacin, moxifloxacin) have been shown to be bactericidal against *M. leprae*.

The commonly used drugs for the treatment of leprosy are dapsone, clofazimine (both bacteriostatic) and rifampicin (bactericidal); others are minocycline, ofloxacin and clarithromycin. Monotherapy with any drug should not be used for fear of early drug resistance.

**Single lesion paucibacillary disease:** Single lesions account for almost 20–80% cases in various parts of India and mainly detected during school surveys and may be cured by a limited amount of chemotherapy. The current regime used for these lesions is termed ROM. ROM consists of single dose of 600 mg of rifampicin, 400 mg of ofloxacin and 100 mg of minocycline administered orally.

**Paucibacillary cases:** Treatment regimen for paucibacillary cases consists of 6 monthly pulses of multidrug therapy to be completed within 9 months. Each pulse is given over a period of 1 month as per following guidelines:

	Age group	
	6–14 years	0–5 years
Rifampicin once a month (supervised)	450 mg	300 mg
Dapsone daily dose (domiciliary)	50 mg	25 mg

**Multibacillary cases:** Treatment regimen for multibacillary cases consists of 12 monthly pulses of MDT to be completed within 18 months.



Each pulse is given over a period of 1 month as per following guidelines:

	Age group	
	10–14 years	6–9 years
Rifampicin once a month (supervised)	450 mg	300 mg
Clofazimine once a month (supervised)	150 mg	100 mg
Clofazimine (self-administered)	50 mg (alternate days)	50 mg (twice a week)
Dapsone once a month (supervised)	50 mg	50 mg
Dapsone daily dose	50 mg	25 mg

Side effects of MDT include flu-like syndrome, acute renal failure, cutaneous reactions, toxic hepatitis, gastrointestinal complaints, hemolytic anemia, methemoglobinemia, thrombocytopenic purpura, disseminated intravascular coagulation and hypotension.

## Treatment of Reactions in Leprosy

Patients undergoing a reversal (type 1) reaction or ENL (type 2) reaction should be observed daily in the early stages and hospitalized if the symptoms are severe, so that sensory loss and deformities are minimized. By repeated reversal reactions, borderline leprosy, and even cases close to LL disease, may be gradually upgraded to TT leprosy, often with disastrous peripheral neuropathy.

Formerly, specific antileprosy therapy was stopped or the dosage reduced during reactions, but these measures are no longer recommended. Damage to eyes and neuropathic changes may ensue rapidly without immediate attention. Nerve tenderness and function must be assessed frequently during reactions. Acute inflammation of isolated lesions without damage to nerves is likely to be of little consequence except for cosmetic considerations.

Without chemotherapy, prognosis in all patients except those with limited and self-healing disease is potentially poor. Patients with borderline or advanced TT leprosy frequently become mutilated because of damage to nerves. Borderline patients can downgrade toward LL leprosy. In patients with LL leprosy, the disease is progressive and can cause death from laryngeal obstruction.

**Reversal reactions:** For reversal reactions, analgesics are given, and the affected area is put at rest. Large daily doses of corticosteroids are started and tapered to a minimal effective dose until the

reaction subsides. Conversion to alternate-day steroid regimens may be attempted when long-term treatment is necessary. Some clinicians use clofazimine for chronic reversal reactions, but it is not recommended for the initial treatment of reactions with acute neuritis. For reactions, clofazimine is probably consistently efficacious only for ENL.

**Erythema nodosum leprosum:** Mild ENL reactions are treated with analgesics; more severe ENL is treated with thalidomide or corticosteroids. Pediatric doses of thalidomide in ENL have not been established, but the initial adult dose is 100 mg 4 times daily followed by a minimal effective dose, usually 100 mg daily. The teratogenic action of thalidomide demands that appropriate measures be taken in the treatment of fertile females. For the rare patient who does not respond to thalidomide or in fertile females, corticosteroids or clofazimine is used. Corticosteroids, if used, are administered in the usual dosage schedules, beginning with large doses and tapering to a minimal effective level. Some clinicians use an alternate-day regimen when long-term steroid therapy is necessary, thus minimizing the well-known side effects. A few studies suggest that pentoxifylline or pentoxifylline plus clofazimine may be effective for ENL. Clofazimine is effective in most patients with ENL and does not have the disadvantages of thalidomide or corticosteroids. The anti-inflammatory action of clofazimine is not manifested until after 4–6 weeks of continuous use. The dosage must be adjusted to the minimal effective level.

### Type 1 reaction:

- **Mild:** NSAID
- **Moderate:** NSAIDs, oral corticosteroids
- **Severe:** NSAIDs, oral corticosteroids

### Type 2 reaction:

- **Mild:** NSAIDs
- **Moderate:** NSAIDs, thalidomide, chloroquine, clofazimine
- **Severe:** Thalidomide, corticosteroids

For type 1 lepra reactions addition of prednisone 1 mg/kg/day orally (40–60 mg) with a slow taper (decreasing by 5 mg every 2–4 weeks after evidence of improvement over 3–6 months) is recommended in addition to standard MDT. If there is evidence of peripheral nerve deterioration, higher doses and longer tapers may be needed, nerve function improves after corticosteroid treatment in 60–70% of patients who did not have preexisting neuritis.

For type 2 reactions in patients older than 12 years of age with systemic symptoms, thalidomide (100 mg/day for 4 days) is the drug of choice. In younger patients or pregnant females in whom thalidomide is contraindicated or in older patients with thalidomide-refractory ENL, corticosteroids may be used in daily doses of 1 mg/kg for 12 weeks. Clofazimine (300 mg/day tapering to <100 mg/day for 12 months) has been useful in managing patients with chronic ENL as well. Lucio's phenomenon is managed with corticosteroids and treatment of underlying infections.

In endemic countries, close monitoring of household contacts of HD patients, particularly those with multibacillary disease and either chemoprophylaxis or early treatment to contacts with evidence of early HD are effective control strategies. A single dose of Bacillus Calmette-Guérin (BCG) vaccine gives variable protective efficacy against leprosy ranging from 28 to 80%; an additional dose demonstrated increased protection. A heat-killed leprosy vaccine, given as an immunotherapeutic adjuvant along with combination MDT, is approved for use in India.

## LONG-TERM COMPLICATIONS

The major chronic complications and deformities of leprosy are caused by segmental demyelination

and permanent nerve injury. The prognosis for arresting progression of tissue and nerve damage is good, if therapy is started early, but recovery of lost sensory and motor function is variable and frequently incomplete. Nerve impairment may be purely sensory, motor, or autonomic, or may be a combination. Sensory deficits lead to undetected trauma, ulceration, and osteomyelitis. Motor deficits result in muscle paralysis, atrophy, and limb deformities, especially of small muscles of the hand and foot (claw hand or foot, foot drop).

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# Marfan Syndrome

## PRESENTING COMPLAINTS

A 9-year-old boy was brought with the complaints of:

- Palpitation since 6 months
- Chest pain since 1 month

## History of Presenting Complaints

A tall slender boy aged about 9 years was brought to hospital with history of palpitation. He was complaining abnormal awareness of the heart-beat. He had noticed that it used to be more on exertion, stress, and strain. He also complained of occasional chest pain on the left side. Chest pain is aggravated by exertion.

## Past History of the Patient

He was the second sibling of consanguineous marriage. He was born at term by normal vaginal delivery. His birth weight was 2.75 kg, length was 52 cm, and the head circumference was 35 cm.

He started to take the breast milk as soon as possible. His developmental milestones were normal. He had been completely immunized. His performance at school was good. He was suffering from repeated respiratory tract infections. He was the tallest boy in the school. He had sore eye problem associated with vision and was corrected by the spectacles.

## EXAMINATION

The boy was moderately built and nourished. He was tall and slender. The extremities were long. The fingers were long and tapered (**Fig. 1**). Anthropometric measurements included, the height was 136 cm (>90th centile), and the weight was 25 kg (50th centile). The arm span was 140 cm.

He was afebrile. The pulse rate was 100 per minute and the respiratory rate was 20 per minute. The blood pressure recorded was 110/60 mm Hg. There was no pallor, no lymphadenopathy, no cyanosis, and no clubbing.

Apex beat was displaced downwards and outward. It was forcible and heaving in character. Diastolic thrill was palpable at right sternal border. High pitched decreased diastolic murmur was

### CASE AT A GLANCE

#### Basic Findings

Height	: 136 cm (>90th centile)
Weight	: 25 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 100 per minute
Respiratory rate	: 20 per minute
Blood pressure	: 110/60 mm Hg

#### Positive Findings

##### History

- Palpitation
- Chest pain

##### Examination

- Tall, thin
- Long extremities
- Displaced apex beat
- Diastolic thrill
- Diastolic murmur

##### Investigation

- ECG: Deep S waves in  $V_1$  and tall R waves in  $V_6$
- Chest X-ray: Showed cardiac enlargement of left ventricular type



**Fig. 1:** Long extremities in Marfan syndrome.

present starting with aortic component of second sound. Other systemic examinations were normal.

## INVESTIGATION

Hemoglobin	: 12 g/dL
TLC	: 7,600 cells/cu mm
ESR	: 20 mm in the 1st hour
ECG	: Deep S waves in V <sub>1</sub> and tall R waves in V <sub>6</sub>
Chest X-ray	: Showed cardiac enlargement of left ventricular type

## DISCUSSION

A tall slender boy with history of palpitation, chest pain and presence of features of cardiac disease puts the diagnosis of Marfan syndrome (MFS).

Marfan syndrome is an autosomal dominant inherited, systemic, connective tissue disorder caused by mutations in the gene encoding the *extracellular matrix* (ECM) protein fibrillin-1 (*FBNI*). The abnormalities are found in elastin and collagen.

It is primarily associated with skeletal, cardiovascular, and ocular pathology. The diagnosis is based on clinical findings, some of which are age dependent.

The disorder shows with high penetrance, but variable expression; both interfamilial and intrafamilial clinical variation is common. There is no racial or gender preference.

The clinical findings of aortic root aneurysm and ectopia lentis (displacement of the lens from the center of the pupil) are particularly important diagnostic criteria because of their specificity and clinical significance.

## PATHOGENESIS

Marfan syndrome is associated with abnormal production, matrix deposition and/or stability of *FBNI*, a 350-kDa ECM protein that is the major constituent of microfibrils, with prominent disruption of microfibrils and elastic fibers in diseased tissues. The *FBNI* locus resides on the long arm of chromosome 15 (15q21), and the gene is composed of 65 exons.

There have been greater than 1,300 pathogenic variants identified in this gene, which are highly penetrant; however, there is a great degree of phenotypic variability with this disorder. A majority of affected individuals (75%) have an affected parent, whereas the rest (25%) are de novo.

Marfan syndrome was traditionally considered to result from a structural deficiency of connective tissues. Reduced fibrillin-1 was thought to lead to

a primary derangement of elastic fiber deposition, because both skin and aorta from affected patients show decreased elastin, along with elastic fiber fragmentation. In response to stress (such as hemodynamic forces in the proximal aorta), affected organs were thought to manifest this structural insufficiency with accelerated degeneration.

### ESSENTIAL DIAGNOSTIC POINTS

- Disproportionate growth
- Skeletal abnormalities
- Arachnodactyly and tall stature
- Joint hyperextensibility
- Lens dislocation and aortic insufficiency
- Mitral valve prolapsed
- Dural ectasia

### GENERAL FEATURES

- Tall stature
- Failure to thrive
- Arachnodactyly
- Mitral valve prolapse
- Aortic regurgitation

## CLINICAL FEATURES (FIG. 2)

The patient is generally tall and slender. Subcutaneous tissue is lacking. Tall stature may be present at birth and persist postnatally. Diminished subcutaneous tissue may suggest failure to thrive. Hypotonia and ligamentum laxity may suggest developmental delay. But cognitive performance is normal. In newborn they present with hypotonia, arachnodactyly, joint laxity and dislocation.

Marfan syndrome is a multisystem disorder, with cardinal manifestations in skeletal, cardiovascular, and ocular systems.

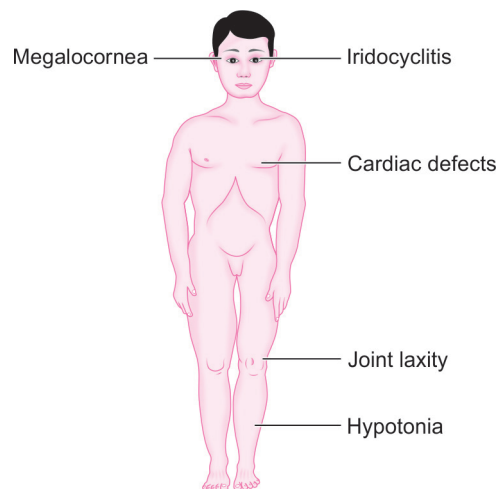


Fig. 2: Clinical features.

## Skeletal System

Excessive bone growth is typically noted in MFS, particularly in the long, tubular bones of the extremities, leading to disproportionally long extremities compared to the trunk (known as dolichostenomelia). This alters the arm span to height and upper to lower segment ratios. The lower segment is measured from the pubic symphysis to the floor, and the upper segment is calculated by subtracting the lower segment from the height. An increased arm span to height ratio ( $>1.05$ ) and a reduced upper to lower segment ratio ( $<0.85$ ) are considered positive findings.

The extremities are long. The lower segment measurement is greater than upper segment measurement. The arm span exceeds the height. The fingers are long and tapered. The wrist sign, i.e., the thumb and the fifth finger when clasped around the wrist is overlapping.

Anterior chest deformity is likely the result of excessive rib growth, pushing the sternum either outward (pectus carinatum) or inward (pectus excavatum). Abnormal curvatures of the spine (most commonly thoracolumbar scoliosis) may also partly result from increased vertebral growth. Other skeletal features include an inward bulging of the acetabulum into the pelvic cavity (protrusio acetabuli), flatfeet (pes planus), and joint hypermobility or joint contractures.

Contracture of the fingers (camptodactyly) and elbows is commonly observed. A selection of craniofacial manifestations may be present including a long narrow skull (dolichocephaly), deep-set eyes (enophthalmos), recessed lower mandible (retrognathia) or small chin (micrognathia), flattening of the midface (malarhypoplasia), a high-arching palate, and downward-slanting palpebral fissures. The recurrent dislocation of the patella is observed. The thumb may be adducted, i.e., Steinberg sign.

Other skeletal features include progressive scoliosis or thoracic kyphosis and abnormally deep acetabulum of the hip known as protrusio acetabuli (which can be associated with pelvic or upper leg pain). Flatfeet (pes planus) as well as a hindfoot deformity defined as medial rotation of the medial malleolus may also be observed in individuals with MFS.

## Cardiovascular System

The major sources of morbidity and mortality from this disorder are the complications noted in the cardiovascular system namely dilation of the aorta, aortic valve insufficiency, aortic aneurysm

and dissection, mitral valve prolapse, tricuspid prolapse, and enlargement of the proximal pulmonary artery.

Within the heart, thickening of the atrioventricular (AV) valves is common and often associated with valvular prolapse. Variable degrees of regurgitation may be present. In children with early onset and severe MFS, insufficiency of the mitral valve can lead to congestive heart failure, pulmonary hypertension and death in infancy; this manifestation is the leading cause of morbidity and mortality in young children with the disorder. Supraventricular arrhythmias and ventricular dysrhythmias may be seen in association with mitral valve dysfunction. Dilated cardiomyopathy occurs with increased prevalence in patients. Aortic valve dysfunction is generally a late occurrence and attributed to stretching of the aortic annulus by an expanding aortic root aneurysm.

The aortic dilation is seen mainly at the level of the sinuses of Valsalva but can be seen in other parts of the aorta as well. The aortic root measurements are interpreted on the basis of normal values for age and body surface area (z-score). Aortic dilatation is progressive over time and, if left uncorrected, increases the risk for dissection in these individuals: however, the onset and rate of progression are highly variable, and hence, close surveillance is warranted by a cardiologist familiar with MFS.

Aortic aneurysm, dissection and rupture, principally at the level of the sinuses of Valsalva (aortic root), remains the most life-threatening manifestations of MFS, promoting lifelong monitoring by echocardiography or other imaging modalities. The most important risk factors for aortic dissection are the maximal aortic root size and a positive family history. The characteristic histologic findings from aortae of patients with MFS include cystic medial necrosis of the tunica media and disruption of elastic lamellae.

Stretching of the chordae tendineae may lead to mitral valvular disease such as mitral valve prolapse. Congestive cardiac failure and rupture of the aorta secondary to the dissecting aneurysm are the common causes of death.

## Ocular System

Dislocation of the ocular lens (ectopia lentis) occurs in approximately 60–70% of patients, although it is not unique to the disorder. Other ocular manifestations include early and severe progressive myopia, flat cornea, increased axial length of the globe, hypoplastic iris, and ciliary muscle hypoplasia, causing decreased miosis. Patients are



also predisposed to retinal detachment and early cataracts or glaucoma.

It is most reliably diagnosed by slit-lamp examination with pupillary dilation. Individuals with MFS are also at increased risk for retinal detachment, glaucoma, and early cataracts.

### Skin Findings

The main skin findings in MFS are stretch marks or striae across the back, shoulders, and inguinal and axillary regions. These individuals can also have widened scars. Individuals with MFS are at risk for hernias, and primary hernia repairs should use synthetic mesh to minimize the risk of recurrence. These findings are not necessarily specific for this disorder.

### Central Nervous System and Dural Manifestations

The dural sac in the lumbosacral region in individuals with MFS can stretch and result in dural ectasia. A majority of patients with this finding are asymptomatic; however, some individuals have pain, weakness, and numbness. This dural abnormality is identified by magnetic resonance imaging (MRI) or computed tomography (CT) scan. Cognitive deficits are not known to be part of the spectrum of MFS.

### Pulmonary Features

The pulmonary features of MFS include spontaneous pneumothorax from lung bullae, reduced pulmonary reserve from pectus deformity or severe scoliosis, obstructive sleep apnea, and emphysematous lung disease.

### Craniofacial Features

The craniofacial features of MFS are notable for a long narrow face with deep set eyes, enophthalmos, downward slanting palpebral fissures, malar hypoplasia, micrognathia, high arched palate, and dental crowding. The facial features are highly variable and not specific to this disorder. However, these individuals can have difficulty with anesthesia and intubation secondary to their craniofacial features.

The disease is most commonly confused with homocystinuria. This may be differentiated by character of the lens dislocation, i.e., upper dislodgement is seen in MFS. In homocystinuria, there is malar flush, generalized osteoporosis and moderate mental retardation. There is positive nitroprusside test and homocysteine is present in urine.

## DIAGNOSIS

Laboratory studies should document a negative urinary cyanide nitroprusside test or specific amino acid studies to exclude cystathionine beta-synthase deficiency (homocystinuria). Although it is estimated that most, if not all, people with classic MFS have an *FBN1* mutation.

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes:

- Rickets
- Chondrodystrophy
- Homocystinuria
- Hereditary arthro-ophthalmopathy
- Lujan syndrome
- Ehlers–Danlos syndrome

## COMPLICATIONS

- Progressive scoliosis
- Astigmatism
- Myopia
- Mitral valve prolapse
- Aortic root dilation
- Aortic aneurysm

## TREATMENT

Treatment includes mainly prevention of complications and genetic counseling. Physiotherapy may improve neuromuscular tone and strength of the affected infants. Maximum exercise should be discouraged. This is because stress increases the cardiac output.

Management of MFS requires a multidisciplinary approach with involvement of different specialists. Yearly ophthalmologic exams are recommended and should be performed by a physician who is familiar with MFS. Most eye problems are controlled with corrective lenses, but some may require surgery. In patients with pectus deformities that interfere with cardiac or pulmonary functioning, a surgical intervention is required. Yearly evaluations for scoliosis and kyphosis are recommended, and it is important to have an orthopedic surgeon involved in the care of these patients.

## Current Therapies

Important advances have been made in the cardiovascular management of patients with MFS. Management recommendations include serial cardiac imaging, medications to decrease progressive aortic root dilation, and prophylactic aortic root replacement. Generally, yearly cardiac

imaging evaluations with echocardiograms alternating with computed tomography angiography (CTA) or magnetic resonance angiography (MRA) are preferred. Due to the fragility of the aorta, contact sports, and isometric exercise are prohibited in individuals with aortic root dilation. Current medical therapies that have been approved to decrease the rate of progressive aortic root dilation include  $\beta$ -blockers and angiotensin II type 1 receptor blockers.

### *Activity Restrictions*

Physical therapy can improve cardiovascular performance, neuromuscular tone, and psychosocial health, and so aerobic exertion in moderation is recommended.

### *Aortic Surgery*

Surgical guidelines for aortic root repair in young children with MFS are determined by: (1) the rate of increase of the aortic root diameter ( $>1$  cm/year), (2) progressive and severe aortic regurgitation, and (3) size of the maximal aortic root (if it exceeds 5 cm). If possible, a valve-sparing procedure is preferred to avoid chronic anticoagulation therapy. However, valvular dysfunction can be seen, which leads to volume overload with resultant heart failure. The leading cause of morbidity and mortality in young children with MFS is mitral valve prolapse, leading to congestive heart failure. It should be noted that children are at high risk for repeat cardiac operations.

### *Pregnancy*

There is higher risk of aortic dissection during pregnancy in women with MFS. Prophylactic aortic root replacement can minimize the risk of aortic dissection and death in women with MFS who wish to become pregnant.

Patients with MFS should continue to receive prophylaxis for bacterial endocarditis, in part because it remains unknown, but possible, that the myxomatous valves typical of MFS are a preferred substrate for bacterial infection.

### **Current Pharmacologic Approaches**

Endocarditis prophylaxis should be started with  $\beta$ -adrenergic blocking drugs such as propranolol, or atenolol.  $\beta$ -blockers have

traditionally been considered the standard of care in MFS and multiple small observational studies suggest there is a protective effect on aortic root growth, with the dose typically titrated to achieve a resting heart rate  $<100$  beats/min during submaximal exercise. Given the putative role of hemodynamic stress in aortic dilation and aortic dissection in MFS, these effects are attributed to the negative inotropic and chronotropic effects of  $\beta$ -blockade.

Deficient extracellular *FBN1* has led to the discovery that myopathy in MFS reflects excessive signaling by transforming growth factor  $\beta$  (TGF- $\beta$ ) an inhibitor myeloblast differentiation. Studies have suggested that aortic aneurysm can be prevented TGF- $\beta$  antagonists including blocker of angiotensin type II/receptors.

### **PROGNOSIS**

The major cause of mortality is aortic root dilation, dissection, and rupture, with the majority of fatal events occurring in the third and fourth decade of life. A reevaluation of life expectancy in MFS suggests that early diagnosis and refined medical and surgical management has greatly improved the prognosis for patients with the condition.

### **GENETIC COUNSELING**

Genetic counseling is mandatory. About 15–30% of the affected individuals are the first born. Paternal age factor is contributing factor. These lead to new dominant mutation with minimal recurrence risk to the future offspring of the normal parents. The heritable nature of MFS makes recurrence risk (genetic) counseling mandatory. Fathers of these sporadic cases are, on average, 7–10 years older than fathers in the general population. This paternal age effect suggests that these cases represent new dominant mutations with minimal recurrence risk to the future offspring of the normal parents. Each child of an affected parent, however, has a 50% risk of inheriting the MFS mutation and thus being affected. Recurrence risk counseling is best accomplished by professionals with expertise in the issues surrounding the disorder.

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# Osteogenesis Imperfecta

## PRESENTING COMPLAINTS

A 7-day-old girl was brought with the complaints of:

- Excessive crying since 3 days
- Swelling in head and leg since 2 days

## History of Presenting Complaints

A baby girl aged about 1 week was brought to hospital with history of excessive crying. Paradoxically, the child was crying a lot when she was consoled by taking close to mother's chest. Her mother noticed the small swellings on the head and along the long bones of both the legs. The mother also told that the swellings were painful and hard in consistency. The child was taking feeds regularly. Her bowel and bladder habits were normal.

## Past History of the Patient

The baby was born at term by normal vaginal delivery. She cried immediately after delivery. The cry of the baby was normal. All the neonatal

reflexes were normal. The weight of the baby was 1.8 kg. The length of the baby was 46 cm and the head circumference was 33 cm. She started taking breast milk immediately.

## EXAMINATION

The child was a low birth weight baby. She was irritable and was lying on the bed and crying. She was crying a lot when she was taken onto the hands. The features of intrauterine growth retardation (IUGR) were present. Anthropometric measurements included, the height was 47 cm (3rd centile), the weight was 1.7 kg (LBW), and head circumference was 33 cm.

The child was afebrile and her heart rate was 126 per minute. Respiratory rate was 26 per minute. The blood pressure recorded was 50/35 mm Hg. There was no pallor, no lymphadenopathy, no cyanosis, and no edema.

The child was lying with broad thigh, fixed at right angles to the thigh. There was beaking of the nose. Short and deformed limbs were present. The child had blue sclera. There were signs of multiple fractures at the swelling sites. The systemic examinations were normal.

## CASE AT A GLANCE

### Basic Findings

Length	: 47 cm (3rd centile)
Weight	: 1.7 kg (LBW)
Temperature	: 37°C
Pulse rate	: 126 per minute
Respiratory rate	: 26 per minute
Blood pressure	: 50/35 mm Hg

### Positive Findings

#### History

- Excessive crying on handling
- Multiple swellings on the head and the extremities
- Low birth weight (LBW)

#### Examination

- Low birth weight
- Excessive crying
- Beaking of nose
- Short limbs
- Multiple fractures

#### Investigation

- *Infantogram*: Multiple old and fresh fractures

## INVESTIGATION

Hemoglobin	: 14 g/dL
TLC	: 7,200 cells/dL
ESR	: 30 mm in the 1st hour
AEC	: 360 cells/cu mm
Infantogram	: Showed evidence of multiple fractures which are fresh and old

## DISCUSSION

It is a rare group of genetic disorders of collagen metabolism and connective tissue, causing bone fragility, with bowing and frequent multiple fractures. The incidence is 1 in 15000.

Osteogenesis imperfecta (OI) (brittle bone disease), the most common genetic cause of osteoporosis. The spectrum of OI ranges from

forms that are lethal in the perinatal period, i.e., OI congenita to a mild form in which the diagnosis may be equivocal in an adult.

## ETIOLOGY

Osteogenesis imperfecta is a primary bone dysplasia. The majority of cases (90%) are caused by autosomal dominant variants in two genes that form type I collagen, COL1A1 and COL1A2. Type I collagen is formed by two COL1A1 and 1 COL1A2 proteins to create a structurally strong triple helix. These large structural proteins contain a helical domain with glycine-X-Y repeats, where X is primarily proline and Y is primarily hydroxyproline.

Structural or quantitative defects in type I collagen cause the full clinical spectrum of OI (types I-IV). Type I collagen is the primary component of the extracellular matrix of bone and skin. These cases are caused by defects in genes whose protein products interact with type I collagen. One group of patients has overmodified collagen, with similar biochemical findings, and other group with collagen structural defects and severe or lethal OI bone dysplasia.

## PATHOLOGY

The collagen structural mutations cause OI bone to be globally abnormal. The bone matrix contains abnormal type I collagen fibrils and relatively increased levels of types III and V collagen. Several noncollagenous proteins of bone matrix are also reduced.

Cortical thickness is reduced in the shafts of long bones and skull bones that are completely surrounded by cranial sutures—wormian bones are present in skull.

Bone cells contribute to OI pathology, with abnormal osteoblast differentiation and increased numbers of active bone resorbing osteoclasts. The hydroxyapatite crystals deposited on this matrix are poorly aligned with the long axis of fibrils, and there is paradoxical hypermineralization of bone.

## PATHOGENESIS

Collagen structural defects are predominantly of two types.

Eighty percent are point mutations causing substitutions of helical glycine residues or crucial residues in the C-propeptide by other amino acids, and 20% are single exon splicing defects.

The clinically mild OI type I has a quantitative defect, with null mutations in 1 alpha (I) allele leading to a reduced amount of normal collagen.

The glycine substitutions in the 2 alpha chains have distinct genotype-phenotype relationships. One-third of mutations in the alpha 1, chain are lethal, and those in alpha 2 are predominantly nonlethal. Two-thirds regions in alpha 1 (I) align with major ligand binding regions of the collagen helix. Lethal mutations in alpha 2(I) occur in 8 regularly spaced clusters along the chain that align with binding regions for matrix proteoglycans in the collagen fibril.

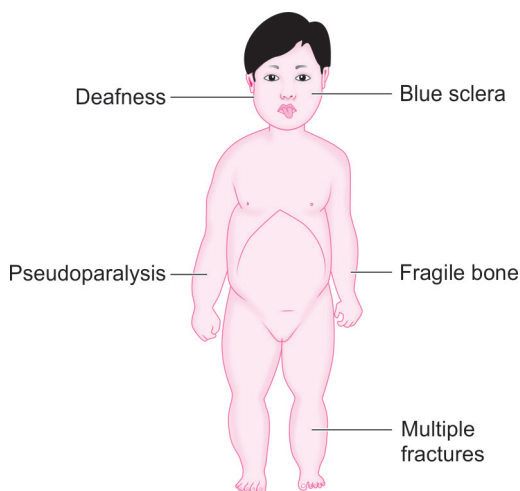
## CLINICAL FEATURES (FIG. 1)

Osteogenesis imperfecta is the most common osteoporotic disease of the newborn. This is characterized by fractures and skeletal deformities. In osteogenesis imperfecta congenita condition, the child dies in newborn period with extreme fragility of bones and numerous fractures. It is distinguished by multiple intrauterine or perinatal fractures.

In osteogenesis imperfecta tarda, the child manifests bone fragility in life and half a normal lifespan. These are genetic syndrome that account for variability.

### Osteogenesis Imperfecta Type I (Mild)

It is of autosomal dominant type, with most cases being familial. Classically, it is defined as non-deforming OI with blue-gray sclera (**Fig. 2**). It is characterized by osteoporosis and excessive bone fragility. The child will have blue sclera. There is presenile conductive deafness.



**Fig. 1:** Clinical features.

Deformities are mainly due to fractures. There are rarely fractures or limb bowing present in utero or at birth. Fractures result from mild to moderate trauma but decrease after puberty. The risk again increases in late adulthood, particularly in postmenopausal women. Vertebral fractures and scoliosis are a risk in childhood and may require therapeutic intervention.

Radiographic features that suggest a diagnosis of type I OI include the presence of Wormian bones in the skull and the finding of generalized osteopenia. Radiograph shows general osteopenia and evidence of previous fracture (**Figs. 3A and B**). Bowing of the lower limb is common. Other possible connective tissue abnormalities include hyperextensible joints, easy bruising, thin skin, joint laxity, scoliosis, wormian bones, hernia, and mild short stature compared with family members.



**Fig. 2:** Blue sclera.  
(For color version see Plate 8)

The diagnosis of type I OI can be made by performing sequence and deletion/duplication evaluation of COL1A1 and COL1A2 or by collagen studies on fibroblasts.

Both types I and IV are divided into A and B subtypes, depending on the absence (A) or presence (B) of dentinogenesis imperfecta.

### Osteogenesis Imperfecta Type II (Fig. 4)

The OI type II is a perinatal lethal form of OI. It is of autosomal recessive type. Biochemically there is marked reduction in the type I collagen, i.e., the principal collagen of bone (**Figs. 5A and B**). It is typically caused by de novo glycine substitutions in COL1A1 or COL1A2. There is severe fragility of the skeleton with consistent findings including the presence of in utero fracture, short and severely bowed extremities, enlarged fontanelles, and low birth length and weight for gestational age. There is deep blue-gray sclera.

Radiograph shows crumpled long bones with fractures and beaded ribs. Multiple rib fractures create a beaded appearance, and the small thorax contributes to respiratory insufficiency.

There is beaking of nose with hypotelorism. Short and deformed bowing of limbs are present. The thighs are broad and fixed at right angles to hip. The legs are held abducted at right angles to the body in the frog leg position. The skull is large for body size, with enlarged anterior and posterior fontanelles. Sclerae are dark blue-gray. The cerebral cortex has multiple neuronal migration and other defects (agyria, gliosis, periventricular leukomalacia).



**Figs. 3A and B:** Osteogenesis imperfecta (type I).  
(For color version (Fig. A) see Plate 8)



Death is typically in the 1st week and caused by respiratory insufficiency as a result of the narrow chest, rib fractures, and potentially the presence of a flail chest. The recurrence risk has been reported to be 6% for de novo changes in OI, given the presence of paternal gonadal mosaicism.

The OI type II is a severe nonlethal form, termed progressively deforming type, and can present with multiple in utero or at-birth fractures and extremity bowing. This type is usually caused by missense variants in COL1A1 or COL1A2. While length may be within the normal range at birth, typically there is reduction to below the normal range by 1–2 years. In infancy, fractures occur frequently from minimal trauma or manipulation. The presence of dentinogenesis imperfecta and scleral color are variable. Radiographic findings include long bone and vertebral anomalies from infancy. Many patients with this subtype are not able to bear weight or ambulate on their own. Orthopedic management, medical management with bisphosphonates, and physical

therapy/rehabilitation care are all required to manage this form of OI. Basilar invagination, caused by compression of the skull on the cervical spine, is common and may progress to brainstem compression, obstructive hydrocephalus, or syringomyelia.

### Osteogenesis Imperfecta Type III

It is of autosomal recessive type. OI type III is the most severe nonlethal form of OI and results in significant physical disability. Birthweight and length are often low normal. It is characterized by severe bone fragility and multiple fractures leading to progressive skeletal deformities. Fractures usually occur in utero. There is relative macrocephaly and triangular facies. Postnatally, fractures occur from inconsequential trauma and heal with deformity. The sclera may be blue at birth and become less blue with age.

Considerate proportion of patients succumb to cardiorespiratory complications in infancy or childhood. The rib cage has flaring at the base, and pectal deformity is frequent. Virtually all type III patients have scoliosis and vertebral compression. Growth falls below the curve by the 1st year. All type III patients have extreme short stature.

Radiograph shows generalized osteopenia and multiple fractures. There is no beading of the ribs and crumbling of the long bones. The skull shows osteopenia and multiple wormian bones. Disorganization of the bone matrix results in a “popcorn” appearance at the metaphyses. Dentinogenesis imperfecta, hearing loss, and kyphoscoliosis may be present or develop over time.



**Fig. 4:** Osteogenesis imperfecta type II.



**Figs. 5A and B:** Osteogenesis imperfecta (type II).

## Osteogenesis Imperfecta Type IV

It is the most common type. It is of autosomal dominant type. It is characterized by osteoporosis. Patients with OI type IV can present at birth with in utero fractures or bowing of lower long bones. They can also present with recurrent fractures after ambulation and have normal to moderate short stature. Most children have moderate bowing even with infrequent fractures. Patients typically have bowing of tibias and have moderate short stature. Children with OI type IV require orthopedic and rehabilitation intervention, but they are usually able to attain community ambulation skills. Fracture rates decrease after puberty. Patients with type IV have moderate short stature. Scleral hue may be blue or white. This form of OI is also typically caused by single nucleotide variants in COL1A1 and COL1A2.

## Osteogenesis Imperfecta Type V (Hyperplastic Callus) and Type VI Hyperosteoridosis (Mineralization Defect)

Types V and VI OI patients clinically have OI similar in skeletal severity to type IV, but they have distinct findings on bone histology. Type V patients also usually have some combination of hyperplastic callus, calcification of the interosseous membrane of the forearm, and/or a radiodense metaphyseal band. They constitute <5% of OI populations. All type V OI patients are heterozygous for the same mutation, which generates a novel start codon for the bone protein. Ligamentous laxity may be present; blue sclera or dentinogenesis imperfecta are not present. Patients with type VI OI have progressive deforming OI that does not manifest at birth. They have distinctive bone histology with broad osteoid seams and fish-scale lamellation under polarized light.

## Osteogenesis Imperfecta Types VII, VIII, and IX (Autosomal Recessive)

Types VII and VIII patients overlap clinically with types II and III OI but have distinct features including white sclerae, rhizomelia, and small to normal head circumference. Surviving children have severe osteochondrodysplasia with extreme short stature.

## Type IX Osteogenesis Imperfecta

It is very rare (only eight cases reported). The severity is quite broad, ranging from lethal to moderately severe. These children have white sclerae but do not have rhizomelia.

### GENERAL FEATURES

- Low birth weight
- Excessive crying
- Beaking of nose
- Short limbs

## DIAGNOSIS

DNA sequencing is the first diagnostic laboratory test; several diagnostic laboratories offer panels to test for dominant and recessive OI. Mutation identification is useful to determine the type with certainty and to facilitate family screening and prenatal diagnosis. It is also possible to screen for type VI OI by determination of serum pigment epithelium derived factor level, which is severely reduced in this type.

Severe OI can be detected prenatally by level II ultrasonography as early as 16 weeks of gestation. OI and thanatophoric dysplasia may be confused. Fetal ultrasonography might not detect OI type IV and rarely detects OI type I. For recurrent cases, chorionic villus biopsy can be used for biochemical or molecular studies. Amniocytes produce false-positive biochemical studies but can be used for molecular studies in appropriate cases.

In the neonatal period, the normal to elevated alkaline phosphatase levels present in OI distinguish it from hypophosphatasia.

Diagnosis is confirmed by collagen biochemical studies using fibroblast cultured from the skin—percutaneous biopsy.

### ESSENTIAL DIAGNOSTIC POINTS

- Dominantly inherited with multiple and recurrent fractures
- Bony deformities growth retardation
- Blue sclera, thin skin
- Hyperextensibility of ligaments
- Otosclerosis with significant hearing loss
- Hypoplastic deformed teeth
- Intelligence not affected

### LABORATORY SALIENT FINDINGS

- Biochemical studies using fibroblast
- Skin—percutaneous biopsy
- Ultrasonographically at 16 weeks
- Chorionic villus biopsy for biochemical assay

## COMPLICATIONS

- *Cardiopulmonary:*
  - Recurrent pneumonia
  - Cardiac failure
- *Neurological:*
  - Basilar invagination

- Brainstem compression
- Hydrocephalus
- Syringohydromyelia

## MANAGEMENT

For osteogenesis type I and type II, no therapeutic intervention is effective. Prompt splinting of the fractures and correction of deformities are recommended. Calcitonin therapy will increase the skeletal mass and decreases the frequency of the fractures.

There is no cure for OI. For severe nonlethal OI, active physical rehabilitation in the early years allows children to attain a higher functional level than orthopedic management alone. Children with OI type I and some with type IV are spontaneous ambulators. Individuals with OI type III are usually wheelchair dependent. With aggressive rehabilitation, they can attain transfer skills and household ambulation.

Children with types III, IV, V, VI, and XI OI benefit from gait aids and a program of swimming and conditioning. Severely affected patients require a wheelchair for community mobility but can acquire transfer and self-care skills. Teens with OI can require psychologic support with body image issues. Growth hormone improves bone histology in growth-responsive children (usually types I and IV).

Orthopedic management of OI is aimed at fracture management and correction of deformity to enable function, fractures should be promptly splinted or cast; OI fractures heal well, and cast removal should be aimed at minimizing immobilization osteoporosis. Correction of long bone deformity requires an osteotomy procedure and placement of an intramedullary rod.

## Hearing Assessment, Regular Dental Check Up

Formal audiologic assessment should be completed at the time of diagnosis, and a computed tomography (CT) or MRI scan should be considered in individuals with severe OI to evaluate for basilar invagination. Twice yearly dental evaluations should be completed starting at age 3. Serum vitamin D should be measured and supplemented if low.

## Bisphosphonates

Geneticist and endocrinologist use bisphosphonates to decrease incidence of fractures. The use of bisphosphonates in OI has been demonstrated

to increase bone density and decrease bone pain, although studies have not clearly shown a reduction in fracture risk (although the studies have significant limitations). Criteria for starting intravenous (IV) bisphosphonate therapy in OI include multiple fractures within 1-year period, the presence of bowing, or the presence of vertebral compression fractures. IV bisphosphonate therapy has also shown benefit in treating bone pain. Although, bisphosphonates improve bone density, it is unclear if they improve bone quality; thus, bisphosphonates should be used cautiously, and the presence of side effects should be closely monitored.

Emerging therapies include teriparatide, an anabolic agent, which was demonstrated to improve density in OI type I, and preclinical antibody therapies against transforming growth factor-B (TGF-B), which has been demonstrated to be upregulated in OI, and an antisclerostin antibody.

## Genetic Counseling

For autosomal dominant OI, the risk of an affected individual passing the gene to the individual's offspring is 50%. An affected child usually has about the same severity of OI as the parent; however, there is variability of expression, and the child's condition can be either more or less severe than that of the parent. The collagen mutation in the mosaic parent is present in some germ cells and may be present in somatic tissues. If a parent is a mosaic carrier, the risk of recurrence may be as high as 50%.

For recessive OI, the recurrence risk is 25% per pregnancy. No known individual with severe nonlethal recessive OI has had a child.

Genetic counseling includes, autosomal dominant have the risk of getting the disease in 50%. Unaffected couple of having the second child as osteogenesis imperfecta is 5–7%.

## PROGNOSIS

Osteogenesis imperfecta limits both the lifespan and functional level.

- *In type II OI:* Die within a month to year.
- *Type III OI:* Reduced lifespan with rehabilitation.
- *Type I and IV:* Compatible with full lifespan.

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## PRESENTING COMPLAINT

A 6-month-old boy was brought with the complaint of deformity of leg since 6 months.

### History of Presenting Complaint

A 6-month-old boy was brought to the hospital with history of deformed legs. Her mother had noticed the deformity at birth. But the concerned doctor assured that it can be corrected by splinting. The mother told that the foot was bent inwards. Whenever, she tried to make the child to stand, the dorsum of the foot was touching the ground. The sole was completely bent inwards.

### Past History of the Patient

The boy was the first child of nonconsanguineous marriage. The boy was born at full term by normal vaginal delivery. He cried immediately after delivery. The birth weight of the baby was 3 kg. Child took breast milk on the 1st day itself. There was no significant postnatal event. Mother had noticed the inward bent of the foot and brought to the notice of the doctor. Doctor had advised splinting and surgery in the later part of childhood.

## EXAMINATION

The child was moderately built and nourished. He was active and alert. He was lying on the bed and playing with the dolls given to him. Anthropometric measurements included, the length was 67 cm (>50th centile), the weight of the child was 7 kg (50th centile), and the head circumference was 40 cm.

Child was afebrile. The heart rate was 106 per minute and the respiratory rate was 22 per minute. The blood pressure recorded was 60/40 mm Hg. There was no pallor, no lymphadenopathy, no cyanosis, and no icterus.

The deformities consist of adduction and rotation of the forefoot. The child's sole was resting on the medial aspect of tibia. There was adduction and external rotation of the bone of the forefoot. Spine and other joints were normal.

## INVESTIGATION

Hemoglobin	: 13 g/dL
TLC	: 7,600 cells/cu mm
ESR	: 32 mm in the 1st hour
Chest X-ray	: NAD
X-ray of the foot	: No significant bony deformities

## DISCUSSION

This deformity is called as talipes. Clubfoot or congenital talipes equinovarus (CTEV) is the term used to describe a deformity involving malalignment of the calcaneotalonavicular complex. Components of this deformity may be best understood using the mnemonic CAVE (cavus, adductus, varus, equinus).

The feathers of this disorder are:

- Plantar flexion of the foot at ankle joint—equinus
- Inversion deformity heel—varus
- Medial deviation of the forefoot—adductus

It is the common foot deformity. It can be congenital, teratologic, or positional. The positional

### CASE AT A GLANCE

#### Basic Findings

Length	: 67 cm (>50th centile)
Weight	: 7 kg (50th centile)
Temperature	: 37°C
Pulse rate	: 106 per minute
Respiratory rate	: 22 per minute
Blood pressure	: 60/40 mm Hg

#### Positive Findings

##### History

- Deformed legs

##### Examination

- Adduction deformity of foot

##### Investigation

- Normal

(or postural) clubfoot is a normal foot that has been held in a deformed position in utero and is found to be flexible on examination in the newborn nursery. The incidence of the deformity is 1:1000. Male to female ratio is 2:1.

It is now considered as multifactorial with single autosomal dominant gene. In majority of the patients, etiology is unknown. It has been suggested that raised intrauterine pressure forces the lower limb of the fetus against the wall of the uterus. This leads to the molding of the feet.

It has been thought alternatively that the deformities are due fiber typed disproportion and increased neuromuscular junction in the muscles of the calf or the soft tissues of the foot. This is the primary neuromuscular cause. All the deformities are secondary to medial dislocation of the talonavicular joint. The atrophy of the calf muscle and foot are more evident in older children.

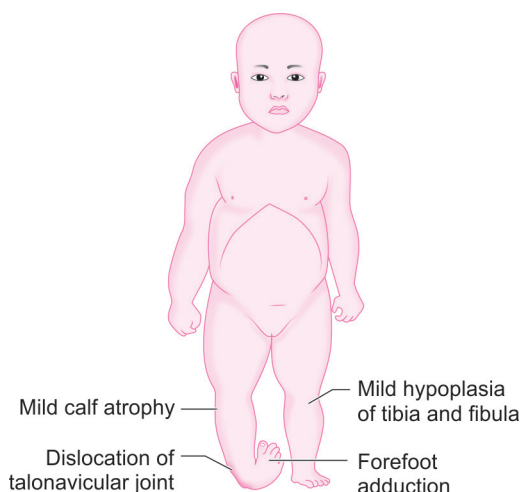
### CLINICAL FEATURES (FIG. 1)

It occurs more commonly in males (2:1) and is bilateral in 50% of cases. The pathoanatomy involves both abnormal tarsal morphology (plantar and medial deviation of the head and neck of the talus) and abnormal relationships between the tarsal bones in all three planes, as well as associated contracture of the soft tissues on the plantar and medial aspects of the foot.

The congenital variety will constitute 75% of the cases. It is characterized by variable rigidity of the foot, mild calf atrophy, mild hypoplasia of tibia, fibula and bones of the feet (**Fig. 2**). Positional clubfoot is normal that had been held in deformed position in uterus.

The congenital clubfoot can either be idiopathic or syndromic. Idiopathic may be hereditary. Congenital clubfoot may be paralytic or secondary to myelodysplasia, the deformities in the arthrogryposis multiplex congenita may also include clubfoot. Sometimes this may be associated with clubbing in the hand. Syndromic clubfoot associated with neuromuscular diagnoses or syndromes is typically rigid and more difficult to treat. Clubfoot is also extremely common in patients with myelodysplasia, arthrogryposis, Larsen syndrome, and other chromosomal syndromes such as trisomy 18 and chromosome 22q11 deletion syndrome.

There will be adduction and external rotation of the bone of the forefoot. The adduction occurs at mid-tarsal and tarsometatarsal joint. The external rotation is produced by torsion of the shaft of the metatarsals (**Figs. 2 and 3**).



**Fig. 1:** Clinical features.



**Fig. 2:** Congenital talipes.



**Fig. 3:** Talipes equinovarus.

The extent of the deformities are variable. In the mildest cases, the deformities consist of adduction and some rotation of the forefoot.



In extreme cases, foot is so deformed that the sole rests on medial aspect of the tibia.

A complete physical examination should be performed to rule out coexisting musculoskeletal and neuromuscular problems. The spine should be inspected for signs of occult dysraphism. Examination of the infant clubfoot demonstrates forefoot cavus and adductus and hindfoot varus and equines. The degree of flexibility varies and all patients will exhibit calf atrophy. Internal tibial torsion, foot length shortening, and leg-length discrepancy (shortening of the ipsilateral extremity) will be observed in a subset of cases.

#### GENERAL FEATURES

- Hand-foot equinus
- Midfoot varus

### DIAGNOSIS

The condition should be diagnosed at birth. Mild deformities may be difficult to distinguish from normal because newborn infants tend to posture the foot in the position of equinovarus. In normal newborn, dorsiflexion occurs till the dorsum touches the anterior aspect of the skin. If this is impossible, the minor degree of talipes exists.

### Radiographic Evaluation

Multiple radiographic measurements can be made to describe malalignment between the tarsal bones. The navicular bone does not ossify until 1–6 years of age, so the focus of radiographic interpretation is the relationships between segments of the foot, forefoot to hindfoot. A radiographic finding is “parallelism” between lines drawn through the axis of the talus and the calcaneus on the lateral radiograph, indicating hindfoot varus. X-ray may be particularly useful for older children with persistent or recurrent deformities that are difficult to assess.

#### ESSENTIAL DIAGNOSTIC POINTS

- Mild calf atrophy
- Mild hypoplasia of tibia and fibula
- Hand-foot equinus
- Midfoot varus
- Forefoot adduction
- Dislocation of talonavicular joint

### DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes:

- Calcaneovalgus feet
- Congenital vertical talus
- Hypermobility pes planus
- Tarsal coalition

### TREATMENT

Nonoperative treatment is initiated in all infants. It should be started as soon as possible following birth. Techniques include taping and strapping, manipulation and serial casting, and functional treatment. It is done between 3 and 12 months of age.

Manipulation of the foot is to stretch the contracted tissues on medial and posterior aspects followed by casting to hold correction is the preferred treatment. Serial casting are typically performed on weekly basis for 6–8 weeks.

Functional treatment, or the “French method”, involves daily manipulations (supervised by a physical therapist) and splinting with elastic tape, as well as continuous passive motion (machine required) while the baby sleeps. Although many feet remain well aligned after surgical releases, a significant percentage of patients have required additional surgery for recurrent or residual deformities. Weekly cast changes are performed; and 5–10 casts are typically required.

If the deformity is slight, foot can be dorsiflexed to little beyond the plantigrade position. The mother should be taught to manipulate her child's foot after every feed. Sufficient pressure should be applied and maintained for about 2 seconds. The pressure is released and reapplied over a period of about 5 minutes.

Splinting can be done by aluminous splint using zinc oxide plaster. The splint is removed and reapplied with little more correction every week. Denis Brown splint may be used throughout the day instead of maternal manipulation until child walks, and thereafter it may be used at night.

Complete correction both clinically and radiologically should be achieved by 3 months. If this happens, holding the cast is then advised for next 3–6 months followed by arthrodesis and correction shoes until the child is walking well.

If there is remaining equinus surgery may be required in the form of percutaneous Achilles tenotomy in order to full correction. After the full correction is obtained, night braces is necessary for long-term maintenance of correction.

Failure of clinical and radiological correction is indication of surgery. About 15–50% require surgical release. The surgical treatment is the complete soft tissue release. This is usually performed between 6 and 12 months of age. The use of tendon transfer and bone procedure including arthrodesis (i.e., fusing), centralization of the tibialis anterior tendon have been useful in young children.

Triple arthrodeses are indicated in painful deformity in adolescence. The most difficult deformity to correct is the hindfoot equinus, and approximately 90% of patients will require a percutaneous tenotomy of the heel cord as an outpatient. Following the tenotomy, a long leg cast with the foot in maximal abduction (up to 70°) and dorsiflexion is worn for 3–4 weeks; the patient then begins a bracing program. An abduction brace is worn full time for 3 months and then at nighttime for 3–5 years. A small subset of patients (up to 20%) with recurrent, dynamic supination deformity will require transfer of the tibialis anterior tendon to the middle cuneiform or recurrence.

Although most patients require some form of surgery the procedures are minimal in comparison with extensive surgical release, which requires lengthening and/or release of muscles and tendons about the ankle and capsulotomy of the major joints to reposition the foot.

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# Glossary

**Absence attack:** These start abruptly in children. A typical attack is not preceded by an aura. There will be brief lapse of consciousness. Patient may show sudden discontinuation of activity with the staring spell, eye fluttering or rhythmic movements. This may last for less than 30 seconds.

**Achondroplasia:** It is an autosomal dominant disease. It is characterized by limb dwarfism, frontal bossing, trident hand and occasionally hydrocephalus. The limb shortening is more in proximal segments. Skeletal radiograph confirms the diagnosis. Genetic counseling is important.

**Acne:** It is a pleomorphic eruption usually seen on the face and trunk. It is observed most commonly during adolescence. It may persist for 1–5 years.

**Acrocephaly:** Skull appears like a turret due to the involvement of all the sutures.

**Acrodermatitis enteropathica:** It is an autosomal recessive disorder usually manifests in the 1st year of life. The causative mechanism is the deficiency of zinc binding ligandin. There will be depigmentation of hair and chronic diarrhea. Administration of zinc sulfate 50–100 mg per day is useful.

**Acromegaly:** This occurs because of hypersecretion of pituitary hormone after the fusion of epiphyses. The child is taller. Peripheral parts of the body like the hands and feet are large. There is prominent jaw, broad nose, enlarged tongue, bushy eyebrows, thick skin and subcutaneous tissue and kyphosis.

**Acute flaccid paralysis:** Acute onset of flaccid paralysis in a child aged <15 years. Poliomyelitis is an important cause.

**Acute phase proteins:** A protein, proteinase inhibitors and coagulase proteins collectively constitute acute phase proteins. They enhance resistance to infection, and promote repair of damaged tissue. These levels fluctuate in response to infection, inflammation and tissue injury.

**Acute tubular necrosis:** There will be dehydration. The oliguric phase lasts for 3–10 days.

The biochemical and clinical abnormalities gradually worsen. Subsequently urine output increases steadily, i.e., diuretic phase. This lasts for a week.

**Adenoid facies:** It occurs as a result of enlarged pharyngeal tonsils. Adenoid facies is characterized by open mouth, narrow, high arched palate and elongated mandible.

**Adrenoleukodystrophy:** It usually presents between the ages of 4 and 12 years. The symptoms include behavioral changes, gait disturbances, dysarthria, dysphagia, loss of vision, seizures and decorticate posturing. One-third of the patients show the evidence of adrenal insufficiency.

**Albinism:** It is an inherited disorder due to the deficiency of enzyme tyrosinase with diminished or absent melanin in skin, hair and eyes. The synthesis of melanin is defective.

**Algid malaria:** The majority of patients with severe malaria remain well perfused and warm. But some may develop shock with cold extremities. This is known as algid malaria. This may result from secondary gram-negative bacteremia and hypovolemia.

**Alport's syndrome:** It is characterized by hereditary glomerulonephritis. It is associated with hematuria and proteinuria. It is also associated with sensory neural deafness. The symptoms include high colored urine, puffiness of the face and generalized edema. Hypertension, urinary tract infection and chronic renal failure are the complications.

**Anemia:** Reduction in the number of red blood cells, the quantity of hemoglobin, and the volume of the packed red cells per 100 mL of blood below normal levels. A hemoglobin level of <11 g/dL indicates anemia in children between 6-month and 6-year-old. The cut of in children older than 6 years is 12 g/dL.

**Anisocytosis:** The term is used to describe an increase in variation in size of the red cells. It may be due to an increase in the number of the small or large cells or both.

*Annular pancreas:* It is due to the failure of complete rotation of the ventral segment during the development. Hence, the collar of the pancreatic tissue surrounds the second part of the duodenum. Usually it does not cause symptoms.

*Anoxic crisis:* This occurs in anemia. The anemia is complicated by leukopenia and thrombocytopenia. This occurs as a result of secondary infection due to anemia.

*Anoxic spell:* It is seen in the tetralogy of Fallot. It occurs predominantly after waking up or after following exertion. The child starts crying and becomes dyspneic. It becomes cyanosed. Convulsions may also occur.

*Antinuclear antibodies:* These antibodies are responsible for a variety of self-antigens. These cause damage to several organs and tissue systems. These produce generalized autoimmune process.

*Apgar score:* It is a semi-objective measure of assessing the infant's respiratory, circulatory and neurological status at birth. Normal babies have an Apgar score of more than 8 at 1 and 5 minutes. The most important cause of cardiopulmonary neurological depression is indicated by low Apgar score.

*Aplastic crisis:* It is caused by sudden cessation of the marrow erythropoiesis. This leads to hemolysis and red cell mass is diminished.

*Apneic spell:* Cessation of respiration for more than 20 seconds or any respiratory pause accompanied bradycardia (heart rate  $<100/\text{min}$ ) and cyanosis.

*Arnold-Chiari malformation:* This refers to extension and displacement of medulla oblongata and cerebellum through the foramen magnum. This malformation may lead to the development of communicating hydrocephalus and clinically may be presented with signs of raised intracranial pressure and respiratory distress because of involvement of lower cranial nerve. Shunting and surgery may be required to treat this condition.

*Arthrogryposis multiplex:* It is a symptom complex characterized by multiple joint contractures present at birth. The involved muscles are replaced partially or completely by fat and fibrous tissue. Most children who have this nonprogressive disorder survive. Some die in infancy as a result of the involvement of the respiratory muscles.

*Ataxia telangiectasia:* It is an autosomal recessive disorder. It is characterized by progressive ataxia, choreoathetosis, pulmonary infection, telangiectasia of the conjunctiva, face and knees. These have

higher chances of developing lymphoreticular tumor. Death occurs due to infection or tumor dissemination.

*Athetosis:* This is one of the types of involuntary movements. These are slow, rhythmic, writhing movements present more in the proximal group under the cover of the hypertonia. The patient is unable to maintain fingers and toes in one position. The lesion is in caudate nucleus and putamen.

*Azotemia:* Retention in the blood of excessive amounts nitrogenous waste products of metabolism. It is a result of failure of the kidneys to remove the urea from the blood; also known as uremia.

*Babinski's sign:* This is one of the methods of eliciting plantar reflex. This is done by stroking along the lateral border of the sole. The normal response is flexion of big and all the toes. The extensor response includes dorsiflexion of the big toe, fanning of the small toes, dorsiflexion of the ankles and contraction of the tensor fascia lata. The causes of extensor response include pyramidal lesion, coma, infancy and postictal.

*Baby mass index:* This is defined as  $\text{wt}/\text{ht}^2$  (in  $\text{kgm}^2$ ). It correlates significantly with subcutaneous and total body fat in adolescents.

*Barlow's test:* This is the provocative test to find dislocation of the hip joint. This is performed by stabilizing the pelvis with one hand and then flexing and adducting the opposite hip, and applying the posterior force. Dislocatable hip readily displaces. After the release of the posterior force, hip usually relocates spontaneously.

*Bartter syndrome:* It occurs as a result from excessive chloride potassium and sodium wasting in the thick ascending limb of loop of Henle. Clinical features include failure to thrive, polyuria, polydipsia and recurrent episodes of dehydration.

*BCG test:* It is more sensitive test than PPD. An induration of more than 6 mm after 3 days of the BCG vaccination is considered as positive reaction.

*Beckwith's syndrome:* It is the syndrome that consists of intractable hypoglycemia. This is seen with the infants with microglossia, large size, visceromegaly, mild microcephaly, omphalocele and facial nevus. It is associated with renal medullary dysplasia. Pancreatic hyperplasia is seen. Some infants also have polycythemia.

*Beriberi:* It occurs as a result of thiamine deficiency, mainly affects the nervous system—dry beriberi, or cardiovascular system, wet beriberi.

In dry beriberi, symptoms include irritability, fatigue, emotional disturbances, headache and polyneuritis. The wet beriberi is characterized by palpitation, tachycardia, dyspnea and edema.

**Bitemporal hemianopia:** Blindness is present in temporal half of both the fields. This occurs in the lesion of nasal halves of both the optic nerves.

**Blackwater fever:** This is characterized by sudden and massive intravascular hemolysis and passage of black colored urine due to hemoglobinuria. In some cases renal failure occur.

**Bloom's syndrome:** It is inherited as an autosomal recessive. Erythema and telangiectasia develop during infancy in a butterfly distribution on the face after exposure to sunlight. A ballooning eruption on the lips and telangiectatic erythema on the hands and forearms may develop. Intellect is normal. Patients usually have low levels of IgA, IgM and IgG. They are susceptible to infections and are sensitive to ultraviolet radiations. Affected children have unusual tendency to develop lymphoreticular malignancies.

**Bronchopleural fistula:** This is one of the peculiar complications to thoracic operation involving resection of lung tissue. This may be due to poor surgical technique and malignant infiltration or tuberculous endobronchitis of bronchial stump. Symptoms appear at the end of 1st week after operation. The symptoms may be fever and blood-stained sputum. Treatment is by early aspiration of the fluid from pleural cavity and by nursing the patient with the affected side down. Smaller fistula can be controlled by aspiration, larger fistula require reopening of the chest and resuturing of the bronchus.

**Brushfield's spots:** It refers to speckled or marbled rash which is found on the iris in Down syndrome.

**Bullous impetigo:** It appears as large fluid-filled blisters which rupture to form superficial erosions. Face, palm and soles are involved.

**Buphthalmos:** It is the congenital rise of intraocular pressure. It should be suspected whenever the anteroposterior diameter and corneal curvatures are increased in size.

**Burr cells:** These are contracted cells which have one or more spiny projections on the surface. These are seen in chronic renal failure.

**Burrow:** Grayish thread like tortuous due to travel of itch mite in the epidermis.

**Cafe-au-lait:** These are uniformly hyperpigmented, sharply, demarcated macular lesions. They are

tan or light brown in color. They vary in sizes and may be large sometimes. Borders are smooth. The lesions are characterized by increasing number of melanocytes and melanin in epidermis. One to three spots are commonly found in normal individuals. They may be present at birth or may develop during childhood. These are present in neurofibromatosis, McCune-Albright syndrome, Russell-Silver syndrome, ataxia, telangiectasia, tuberous sclerosis and Bloom's syndrome.

It helps in determining  
hypertelorism.

It is calculated by

$$\text{Canthal index} = \frac{\text{Inner canthal distance}}{\text{Outer canthal distance}} \times 100$$

This is normally 38 in males, and 38.5 in females. This index is increased in hypertelorism.

**Capillary hemangioma:** This refers to congenital abnormalities of vessels. These are of three types. There can be salmon patch, port-wine stain and strawberry angioma. They are present over the forehead and over the occiput. They disappear by 1 year.

**Caput succedaneum:** It is the edema of the scalp that follows local pressure and trauma during delivery. It is soft, pits on pressure. It is not fluctuant. It does not have well-defined margin.

**Carey Coombs murmur:** It is the delayed diastolic murmur heard during the course of acute rheumatic fever. This occurs as a result of pancarditis.

**Caries:** A microbial disease resulting in demineralization of inorganic material and destruction of organic content of the hard tissues of teeth.

**Carpenter syndrome:** Here craniosynostosis is associated with mental retardation and preaxial polysyndactyly of the feet. Soft tissue syndactyly of hands is also present. Patella is displaced.

**Carrier:** Presence of specific infectious agent in the absence of clinical disease. A carrier serves as potential source for the further transmission. Temporary carrier lasts less than 6 months. Chronic carrier state may last lifelong.

**Cellulitis:** It is a spreading inflammatory exudate along subcutaneous and facial planes. The most common causative organism is *Streptococcus pyogenes*. Redness or itching or stiffness commences followed by tenderness and swelling. The skin becomes shiny in appearance. Local gangrene may occur. Appropriate antibiotics and rest are the mainstay of treatment.



*Cephalhematoma:* It is the subperiosteal hemorrhage usually involves parietal and temporal bones. It depends on obstetric maneuvers. It is more frequent with forceps delivery vacuum extraction and prolonged labor.

*Chemosis:* This is edema of conjunctiva, due to orbital cellulitis, nephritis, angioneurotic edema or cavernous sinus thrombosis.

*Cherry red spot:* This is the round bright white area at the macula whose center is occupied by cherry red circular spot. It is seen in Tay-Sachs disease, gangliosidosis, Niemann-Pick disease.

*Cheyne-Stokes breathing:* It is a periodic breathing indicates bilateral damage to cerebral cortex with an intact brainstem. It is attributed to an abnormally increased ventilatory response to  $\text{CO}_2$  followed by posthyperventilation apnea.

*Chloromas:* These are the localized collection of leukemic cells seen almost exclusively in patients with acute myeloid leukemia. They may occur at any site including CNS, bones and skin.

*Cholesteatoma:* It is a sac of squamous epithelium extending from tympanic membrane to middle ear.

*Chorea:* It is the purposeless jerky movements, resulting in deranged speech and muscular incoordination. This results in awkward gait and weakness. This involves commonly distal muscles under the cover of hypotonia. The lesion will be in putamen and caudate nuclei. They are increased by agitation, decreased by voluntary activities and disappear during sleep. The causes are rheumatic fever, typhoid, thyrotoxicosis, Wilson's disease and drugs.

*Choreoathetosis:* It is characterized by sudden onset of unilateral or bilateral dystonic posturing of the leg or arms. It is associated with facial grimacing and dysarthria. This is precipitated by sudden movements particularly on rising from sitting posture. It is typically seen between 8 and 14 years. It can be managed by anticonvulsants.

*Clinodactyly:* This is deviation of deflection of the fingers seen in Down's syndrome and trisomies.

*Clutton's joint:* This condition is due to bilateral effusion developing in knee joint. This is usually seen in congenital syphilis and is painless.

*Coeur-en-sabot:* Here the absence of the main pulmonary artery segment makes heart shadow resembling that of the boot. Hence it is called as coeur-en-sabot. The right ventricle is enlarged and is prominent. This occurs in tetralogy of Fallot.

*Cold chain:* A series of events undertaken to maintain the vaccines at a lower temperature from the manufacture to the place of administration to maintain efficacy.

*Conn syndrome:* It is characterized by episodic and reversible weakness. Proximal myopathy may become irreversible. CPK levels are elevated. Myoglobinuria occurs in acute attacks.

*Coxa vara:* It is deformity of the hip joint with decrease in angle of inclination between neck and shaft of the femur.

*Craniotabes:* This occurs because of reduction in mineralization of the skull. This results in abnormal softness. This is evident in parietal and occipital bone. This is seen characteristically in rickets.

*Crigler-Najjar syndrome:* It is inherited as an autosomal recessive. It is characterized by hyperbilirubinemia type II is autosomal dominant. It responds to treatment with phenobarbitone.

*Crohn's disease:* It is one of the inflammatory diseases characterized by abdominal mass, strictures, and fistulae. The lesion is characterized by skip lesions and transmural involvement. Erythema nodosum and mouth ulcers are common. The most common place of involvement is ileum. The aim of the treatment is to alleviate the symptoms. Oral prednisolone may be tried. Surgical therapy involves bowel resection if there is high recurrence rate. Nutritional therapy is the effective primary treatment.

*Crouzon syndrome:* It is characterized by acrocephaly, hypertelorism, exophthalmos, hypoplastic maxilla, beak-shaped nose short upper lip and protruding lower lip. It is autosomal dominant.

*Cryptorchidism:* It can be due to imperfect descent of the testes. This can also be incomplete descent or ectopic. Many a times, testes will be retained within the abdomen, in the inguinal canal or in superficial inguinal pouch. Treatment is by orchiopexy.

*Cubitus valgus:* It is deformity of hip joint with increase in angle of inclination between neck and shaft of the femur.

*Cysticercosis:* It is the infection with intermediate stage of, i.e., larva of *T. solium*. Neurocysticercosis is the most common parasite infection of the CNS. The common target organ for cysticercosis are brain, muscle and subcutaneous tissue.

*Cystinosis:* It is the autosomal disorder presents in infancy. Affected patients later show photophobia,

enlarged liver and spleen, blonde hair. Presence of the cystine crystals in cornea and elevated levels of leukocyte cystine is useful in diagnosis.

*Cystinuria*: It is the metabolic disorder with autosomal recessive inheritance. There is selective increase in the renal clearance and urinary excretion of the basic amino acids.

*Dacryoadenitis*: It is an acute bilateral inflammation of lacrimal gland. Occurs with influenza, mumps and infectious mononucleosis. Chronic dacryoadenitis is associated with syphilis, tuberculosis and sarcoidosis.

*Dandy-Walker syndrome*: In this syndrome, there is cystic dilatation of the fourth ventricle leading to congenital hydrocephalus. This causes obstruction of the foramina of Magendie and Luschka. The associated anomalies include agenesis of the posterior cerebellar vermis and corpus callosum. There will be a rapid increase in the size of the head and transillumination test is positive. It is managed by shunting the cystic activity.

*Darting tongue*: Here child cannot maintain the tongue in protruding position, i.e., darting tongue. This is seen with Sydenham's chorea.

*De musset's sign*: It is nodding of the head. It may be present with each systole due to the sudden filling of the carotid vessels in severe aortic regurgitation.

*Delinquency*: Neglecting a legal obligation; failing to do in accordance with law.

*Dermatomyositis*: This is the collagen disease characterized by nonsuppurative inflammation of the skin, subcutaneous tissues and muscles. There will be necrosis of muscle fibers. Oral corticosteroids such as prednisolone, cyclophosphamide are used. Physical and occupational therapy is also important.

*Development*: Increase in capability or maturation of function. It is related to maturation and myelination of the nervous system and acquisition of variety skills for variety of functioning of the individual.

*Digeorge syndrome*: This is characterized by defects in embryogenesis of the third and fourth pharyngeal pouches. It presents with unusual facies, hypocalcemia tetany, aortic arch anomalies and an absent thymus.

*Disseminated intravascular coagulation*: This is serious disorder where the blood gets coagulated within circulation, using up coagulation factors and platelets.

*Dolichocephaly*: This occurs due to premature closure of the sagittal suture. The skull grows perpendicular to the open coronal suture. It appears to expand anteroposteriorly in the direction of the sagittal sutures.

*Doll's eye response*: If the head is suddenly turned to one side, there is conjugate deviation of the eye in the opposite direction. This response occurs if the brainstem is intact. It is not seen in normal conscious infants. It is absent when the brainstem centers for eye movements are damaged.

*Double-bubble sign*: It is the type of gas shadow seen on plain abdominal radiograph. The appearance is caused by distended and gas-filled stomach and proximal duodenum. This is seen in duodenal atresia.

*Dubin-Johnson syndrome*: It is an autosomal recessive disorder of childhood characterized by elevated level of conjugated bilirubin. This presents as an intermittent obstructive jaundice. There will be elevated levels of coproporphyrin in the urine.

*Duchenne muscular dystrophy*: It is the most common hereditary neuromuscular disease. It is a X-linked recessive trait. It is characterized by proximal muscle weakness. Respiratory muscle involvement is expressed by weak cough, recurrent lung infections. There will be pseudohypertrophy of calf muscles. The CPK and LDH levels are consistently elevated.

*Duodenal stenosis*: Stenosis occurs at the point of fusion of fore and midgut. It is frequently accompanied by other congenital anomalies. Laparotomy should be undertaken. Duodenojejunostomy is done.

*Duroziez's sign*: A systolic murmur may be heard if the pressure is applied to partially occlude the artery proximal to the chest piece. The diastolic murmur is heard if the pressure is applied distally. This combination of systolic and diastolic murmur is the Duroziez's sign.

*Dysostosis multiplex*: It is characterized by dolichocephalic skull with thickened calvarium. Medial third of the clavicle is thickened. There will be tapering of the phalanx. This is seen in mucopolysaccharidoses.

*Dysphoria*: It is a disorder of the mood. It consists of major depression, dysrhythmic disorder and bipolar disorder.

*Dystonia*: It is the slow intermittent twisting motion. This produces exaggerated turning and

posture of the extremities and trunk. The principal causes include perinatal asphyxia, dystonia musculorum deformans, Wilson's disease and drugs such as L-dopa, lithium.

*Ebstein anomaly*: In this anomaly, tricuspid valve is set into right ventricle. This creates a large square-shaped heart. There is downward displacement of tricuspid valve. It is associated with Wolff-Parkinson-White (WPW) syndrome and supraventricular tachycardia. Treatment is by prostaglandin infusion.

*Ecchymosis*: A large superficial hemorrhage, usually blue in color. These are seen platelet count less than 50,000/cu mm.

*Eczema*: Infantile eczema manifests as a rosy erythema over the cheeks. There is brawny desquamation, small papule formation and some crusting. Most children show a resolution by the age of 1 or 2 years. But the illness may continue with remission and exacerbation in few cases.

*Edward syndrome*: It is the second most common autosomal trisomy. Majority of the cases are premature with low birth weight. These are hypertonia, elongated skull, lowest and malformed ear, micrognathia, shield-shaped chest. The mean survival is about 3 months.

*Ehlers-Danlos syndrome*: The basic manifestation are joint hypermobility, skin hyperextensibility, dystrophic scarring of the skin and easy bruising and connective tissue fragility. Wound healing is delayed and there is free movable subcutaneous nodules.

*Eisenmenger syndrome*: It is the cyanotic heart disease with pulmonary arterial hypertension. This results in right to left shunt at the atrial, ventricular or pulmonary arterial level.

*Encephalocele*: It is the herniation of brain and meninges through the defect in calvaria.

*Endocardial fibroelastosis*: This is thickening of the endocardium. This presents with cardiac failure in infancy. Aortic stenosis, aortic atresia, hypoplastic left heart syndrome are the causes. Dyspnea, cough, anorexia, hepatomegaly, edema are the manifestations.

*Enuresis*: It is defined as normal nearly complete evacuation of the bladder at a wrong place and time at least twice a month after the 5th year of life.

*Epidermolysis bullosa*: It is an autosomal recessive condition. It is life-threatening. Serum morbidity and disfigurement can occur as a result

of complications. Blisters appear at birth and involves perioral, scalp, legs, diaper area. Healing is delayed. Mild atrophy may be seen in area of recurrent blisters. Most patients die in first 3 years of life.

*Epidermolysis hyperkeratosis*: It is inherited as an autosomal trait. Onset is at birth. There is generalized erythroderma and severe hyperkeratosis. The scales are small, hard and verrucous and distinctive. Hyperkeratosis persists throughout the adult life. Recurrent blistering is present. Palms and soles are thickened. Some may have crumpled ears and ectropion. Treatment is difficult. Oral antibiotics, keratolytic agents and oral retinoids are useful.

*Epstein pearl*: These are epithelial inclusion cysts appear as whitish spots on the hard palate. No treatment is required.

*Erythema infectiosum*: It is also called as fifth disease most common manifestation of the human parvovirus infection. The characteristic skin lesions occur in three stage.

*Erythema marginatum*: It is a type of skin discoloration showing red areas. These are disc-shaped with elevated ridges. It is one of the major criteria of acute rheumatic fever.

*Erythema multiforme*: The most important characteristic is an acute target lesion. This may appear erythematous, macular, urticarial, papular, vesicular or bullous. This is believed to be an immune complex disease.

*Erythema toxicum*: On the second and 3rd day of the newborn, these appear as discrete, erythematous papules may appear on trunk and face. The rash disappears spontaneously in 1-3 days.

*Erythropoiesis*: This is the term used to describe development of nucleated red cells. It is characterized by diminution in cell size, ripening of cytoplasm and ripening of muscles.

*Esophageal atresia*: It is usually associated with tracheoesophageal fistula. Child may regurgitate; saliva pours, coughing and cyanosis occur on feeding.

*Exostosis*: It occurs due to failure of bone remodeling at metaphysis. A variable number of extra growths develop at the metaphyseal region. These may stop growing at the completion of the skeletal growth.

*Failure to thrive*: Weight for the age less than two SD or below 3rd centile or downward change

in growth that has crossed two major growth percentile (i.e., 75th percentile to below 25th percentile) in a short time.

*Fallot's tetralogy:* It is associated with infundibular obstruction, overriding of aorta, ventricular septal defect and right ventricular hypertrophy. Cyanosis is present at birth which deepens on crying. Anoxic spell occurs. Medical management is limited to treatment of complications and correction of anemia.

*Fanconi's anemia:* It is an autosomal recessive disorder. It is characterized by congenital malformation of bones of forearm, short stature and mental retardation. There will be hyperpigmentation, cafe-au-lait spots. The main complications are liver disorders, infection and bleeding.

*Flag sign:* It is characterized by bands of pigmented and depigmented zones of hair present in malnutrition especially kwashiorkor.

*Floppy infant:* It is described as an infant with marked hypotonia of all the muscles. They may be associated with frequent respiratory infection, feeding difficulties, facial weakness. Contractures may develop in later stages.

*Foster Kennedy syndrome:* This is seen with intracranial spaces-occupying lesion. There may be optic atrophy in the fundus in the same side and papilledema in the opposite side.

*Friedreich's ataxia:* It is due to autosomal recessive inheritance. It presents usually in late childhood. There is progressive dysfunction of cerebellum and spinal cord. Patient can have myocarditis, cardiac failure, kyphosis, scoliosis, hammer toes and diabetes mellitus.

*Froehlich syndrome:* It is characterized by obesity, short stature hyperphagia, sexual infantilism and sometimes blindness.

*Furunculosis:* It is an acute infection of hair follicle which usually precedes suppuration and necrosis. A painful indurated swelling appears which gradually extends. After 2 or 3 days, the center softens and a small slough is discharged. It is common on back of the neck.

*Gallop rhythm:* It is an auscultatory finding of the three of four heart sounds. The extra sound is heard in diastole. It is related either to atrial contraction or to rapid filling of ventricle.

*Genetic counseling:* It is a communication process, dealing with human problem associated with occurrence and recurrence of genetic disorder in a family. Patients should be provided with

risk figures for future offspring based on genetic facts.

*Gigantism:* Hypersecretion of the growth hormone in children, usually due to pituitary adenoma results in the somatic overgrowth or gigantism. The child is taller than his peers. Peripheral parts of the body like hands and feet are large. Muscle weakness, bony and cartilaginous overgrowth, cardiomyopathies may be present.

*Gliosis:* It is the excess of astroglia seen in damaged area of central nervous system.

*Gower's sign:* This is seen in Duchenne's muscular dystrophy. Here child turns to side, lifts his trunk up by supporting his weight on his arms and then stands as if he is climbing upon his arms and is standing up.

*Grasp reflex:* When the baby's palm is stroked with the examiners index finger, baby's fingers close on it and grasp it. As the examiner lifts his index finger, the flexor muscles of infants forearm become tight. The grasp reflex usually disappears by the age of 12 weeks. Persistence beyond this age should arouse the suspicion of brain damage.

*Graves' disease:* It is the toxic goiter. It occurs due to the presence of thyroid stimulating autoantibodies. This binds to the receptor of thyroid stimulating hormone. The ophthalmopathy is caused by antibodies that bind to the extraocular muscles and orbital fibroblasts.

*Greenstick fracture:* Here one cortex may be fractured, while the other bends. The resultant angulation may be hard to correct without completing the fracture. This type of fracture is more common in children.

*Grey-Turner's sign:* It is dark discoloration around umbilicus seen in pancreatitis.

*Growth:* It is the net increase in mass of tissues, due to multiplication of cells and increase intracellular substance

*Guillain-Barré syndrome:* It is a postinfection polyneuropathy. This causes demyelination in motor and sometimes in sensory nerves. The paralysis of muscles occurs. Weakness begins in lower limbs and extends upwards. CSF protein is increased. Treatment is self-limiting and symptomatic.

*Guthrie's test:* It is the microbiological test based on the principle that phenylalanine is necessary for growth of the *Bacillus subtilis*.

*Gynecomastia:* It is occurrence of mammary tissue in male. It is almost always a sign of the

estrogen-androgen imbalance. The main causes include physiological changes, Klinefelter's syndrome, ketoconazole drugs, and Peutz-Jeghers syndrome.

*Harrison's groove:* It is a horizontal depression, seen along the lower border of chest corresponding to insertion of the diaphragm. This is seen in rickets.

*Head banging:* It involves rhythmic hitting of the head against the solid surface. It results in callus formation at the site of banging abrasion and contusion.

*Hemangioma:* Vascular lesions on the skin. These can be superficial (strawberry) or deep (cavernous). These are primarily composed capillaries. Most are situated on head and neck.

*Hemarthrosis:* This is seen in hemophilia. It may occur spontaneously but usually results from minor joint strain or from a direct injury. This happens during active phase of bleeding. The pain and disability depends upon rapidity and duration of bleeding.

*Hemianopsia:* Here one half of the visual field is lost. It can be homonymous, bitemporal or binasal.

*Hemiparesis:* It is associated with decreased arm swing on affected side and lateral circular motion of leg.

*Hemochromatosis:* It is disorder of iron metabolism with excess deposition of iron in tissues leading to bronze skin pigmentation, hepatic cirrhosis and diabetes mellitus.

*Hemolytic uremic syndrome:* It is characterized by acute renal failure, microangiopathic hemolytic anemia and thrombocytopenia. It is the most common cause of acute renal failure (ARF). Onset is preceded by gastroenteritis, pallor, irritability, weakness and oliguria. The complications include acidosis, anemia, cardiac failure, hypertension and uremia. Peritoneal dialysis and management of hematological and renal manifestations are recommended.

*Hemopoiesis:* It is the formation and development of blood cells. This can be either extramedullary as in spleen, liver and lymph nodes.

*Hemoptysis:* It means presence of blood-stained sputum. Many times it is confused with hematemesis. The causes of this are tuberculosis, bronchiectasis, whooping cough, pneumonia, mitral stenosis and bleeding disorders.

*Hiatus hernia:* It may be acquired or congenital. There are three types: sliding, paraesophageal and

mixed. Pain, heart burns, dysphagia and secondary anemia may be present.

*Hills sign:* It is the *exaggeration* of systolic pressure difference between the brachial and femoral arteries, seen in aortic regurgitation.

*Hirschsprung's disease:* It is congenital megacolon characterized by absence of ganglion cells of myenteric plexus. There will be delayed passage of meconium. Failure to pass stool leads to dilatation of proximal bowel and abdominal distension. Rectal manometry and rectal suction biopsy are the most reliable indicators. Surgery is the treatment of choice.

*Histiocytosis:* Here there will be prominent proliferation or accumulation of monocyte-macrophage system of bone marrow origin. The diagnostic classification depends on histopathological findings. The clinical manifestations vary. Bone involvement, skin involvement, exophthalmos, pituitary dysfunction, weight loss are present. Immunosuppressive therapy includes cyclosporine and antithymocyte globin.

*Hodgkin's disease:* This is a type of lymphoma where normal architecture of lymph node is distorted. The lymph nodes contain giant cells with mirror image nuclei called Reed-Sternberg cells. These cells are associated with painless enlargement of lymph nodes and hepatosplenomegaly with fever. Treatment is by chemotherapy.

*Homocystinuria:* It is a metabolic error with autosomal recessive inheritance. Cystathionine is not synthesized from the homocysteine and serine because of the deficiency of enzyme cystathionine synthetase.

*Horner's syndrome:* There will be sinking of eyeball, ptosis of upper lid, slight elevation of lower lid, miosis, narrowing of palpebral tissue and anhidrosis and flushing of affected side of the face. This is due to paralysis of cervical sympathetic nerves.

*Hutchinson's teeth:* These are also called screw-driver teeth. This is seen in children with congenital syphilis. The upper edge of incisor is centrally notched and widely spaced.

*Hyphema:* It is the presence of blood in anterior chamber of the eye. It may follow either blunt or perforating injury. It appears as a bright or dark red fluid level between cornea and iris. Treatment is by rest.

*Hypospadias:* It is the most common congenital anomaly of the urethra. The external meatus is situated at some point under the surface of penis or



in perineum. The types include glandular, coronal, penile, penoscrotal and perineal.

*Hypotonia*: It is characterized by flabby muscles which offer less resistance to passive movements.

*Hypoxic ischemic encephalopathy*: It refers to CNS dysfunction associated with perinatal asphyxia.

*Ichthyosis*: It is an inherited keratinizing disorder of the skin associated with distinct pattern of visible scaling. These are hyperproliferative and retention type.

*Imperforate anus*: It occurs as a result of imperfect fusion of postallantoic gut with proctodeum. These are of two types, high and low, depending upon termination of bowel above and below the pelvic floor. Surgery is the treatment.

*Impetigo*: It is a superficial bacterial skin infection involving the upper epidermis. There are two types, i.e., nonbullous and bullous type.

*Interferons*: These are the proteins produced and secreted by blood leukocytes, fibroblasts and epithelial cells. These influence many cell functions. These include restoration, augmentation and/or modulation of hosts' immune system.

*Jaw thrust*: It is used for victims of the neck injury and can be accomplished without extending the neck. Fingers of each hand are placed under the sides of lower jaw to lift it up and outward.

*Jitteriness*: Symmetrical tremulous movements of the extremities more proximal than distal, suggests cerebral hyperexcitability or metabolic defect such as hypoglycemia.

*Kangaroo mother care*: It is a powerful easy to use method to promote the health and wellbeing of low birth weight babies. Its key features include early continuous prolonged skin to skin contact between the mother and baby.

*Kartagener's syndrome*: This is a hereditary syndrome associated with dextrocardia, bronchiectasis and sinusitis. Immobile cilia are also present in this condition. It is characterized by recurrent otitis media, conductive hearing, deafness and loose productive cough. Treatment is symptomatic.

*Keratoconus*: It is conical cornea in which cornea is thin near the center and progressively bulges forward. It is present in Down syndrome, Marfan's syndrome and osteogenesis imperfecta.

*Keratomalacia*: Here the cornea is softened and ulcerated. It is usually irreversible and results in scar formation or phthisis bulbi.

*Kernicterus*: The term is used to describe the pathological finding of bilirubin toxicity within the brain. This includes staining and necrosis of neurons.

*Kernig's sign*: This is usually seen in meningitis and refers to an inability to completely extend the leg when sitting or lying with the thigh flexed upon the abdomen.

*K-F ring*: This is seen in Wilson's disease. It occurs because of the golden brown deposits of copper in the Descemet's membrane of the cornea.

*Knock-knee*: It is a deformity of thigh or leg or both the knees. The knees are abnormally close together and space between the ankles is increased. This is seen in rickets.

*Koilonychia*: This is dystrophy of fingernails in which they are thin and concave with the raised edges. This is present in iron-deficiency anemia.

*Koplik's spots*: These are grayish or bluish white grain rashes seen inside the cheek opposite to upper molar. These are seen in measles.

*Kussmaul breathing*: This is characterized by deep rapid respiration. This is seen in diabetic ketoacidosis.

*Kyphosis*: It is an abnormally increased convexity in curvature of thoracic spine as viewed from the side.

*Larva migrans*: It is caused by nematodes that are normally parasitic for other species, the larva hatch and invade the intestinal mucosa to be carried by bloodstream to different organs.

*Laurence-Moon-Biedl syndrome*: It is characterized by pleomorphic pigmentary retinal degeneration with a progressive vision impairment. There will be prominent macular involvement. Obesity is one of the clinical features.

*Legg-Perthes syndrome*: It is an idiopathic avascular necrosis of the hip joint. It is caused by interruption of blood supply. It is associated with protein C, protein S, thrombophilia and hypofibrinolysis. Children with this syndrome will have delayed bone age, disproportionate growth and mild short stature.

*Lennox-Gastaut syndrome*: It is characterized by mixed seizure including myoclonic, atypical absence generalized tonic-clonic or partial seizures.

*Lepromin test*: It is carried out by injecting 0.1 mL of Mitsuda lepromin intradermally onto the forearm and reaction is noted later at 21 days.

*Live-born:* It is the product of conception irrespective of weight or gestational age that after separation from the mother, shows any evidence of life such as breathing, heart rate, pulsation of the umbilical cord or definite movement of voluntary muscle.

*Loeffler's syndrome:* The pulmonary phase of migration of ascaris larva may cause wheezing, pulmonary problems and eosinophilia in blood.

*Lorber criteria:* This is for surgical treatment for neural tube defects. Surgery is not done if there is severe paraplegia at or below L3 level, kyphosis or scoliosis, gross hydrocephaly.

*Lordosis:* It is forward curvature of lumbar spine.

*Lowe syndrome:* This is X-linked condition presents within the first few months of life with Fanconi syndrome, rickets, ocular defects, hypotonic and developmental delay.

*Macewen's sign:* It is a hyperesonant note heard on percussion of skull behind junction of the frontal, temporal and parietal bones. This is seen in hydrocephalus, cerebral abscess and in raised intracranial tension.

*Mantoux reaction:* 0.1 mL of a suitable dilution of tuberculin is injected intradermally. A swelling of 5 mm should be raised. The reaction is read after 48 hours.

*Marasmus:* It is characterized by gross wasting of muscle and subcutaneous tissues resulting in emaciation, marked stunting and no edema.

*Marfan's syndrome:* It is an autosomal dominant disorder with mesodermal dystrophy. The patients are tall and slender. Muscles are hypotonic and joints are hyperextendable. There may be subluxation of lens, cataract, coloboma, squint, nystagmus and megalocornea.

*McBurney's point:* It lies at the junction of lateral third with medial two-thirds of line joining anterosuperior ilial spine and the umbilicus. It is the classical site of the greatest tenderness in appendicitis.

*McCune-Albright syndrome:* This is also called polyostotic fibrous dysplasia. This disease is characterized by precocious puberty in female, melanotic pigmentation of skin, hyperthyroidism, epileptic seizures, headache and mental derangement.

*Meckel's diverticulum:* It is remnant of embryonic yolk sac. It is also referred as omphalomesenteric duct or vitellointestinal duct. Partial or complete failure of involution results in residual structures.

Meckel's diverticulum is one such structure. It presents with brick colored or currant jelly stool. This is painless. Sometimes, it may be associated with partial or complete bowel obstruction.

*Megalecephaly:* It is also called hydrocephalus. It represents diverse group of conditions that result from impaired circulation and absorption of CSF. Sometimes it can be due to choroid plexus papilloma.

*Megalocornea:* Here the corneal diameter is more than 13 mm. It is observed in Marfan's syndrome and osteogenesis imperfecta.

*Meningeal tuberculosis:* This is also called tuberculous meningitis. This is characterized by meningeal sign, headache, vomiting and convulsion. The CSF analysis should be done. The treatment is antitubercular medicines.

*Meningococemia:* This occurs as a result of meningococcal infection. It will vary from fever to occult bacteremia to sepsis, shock and death.

*Mental retardation:* Significant subaverage intellectual function with intellectual quotient (IQ) <2 SD below the mean. It is associated deficits in adaptive behavior.

*Metachromatic leukodystrophy:* The inheritance is autosomal recessive. The characteristic metabolic defect is decreased urinary or leukocyte aryl sulphatase. Clinically it manifests as ataxia, stiffness starting in the 2nd year of life.

*Metaphysis:* It is the wider part at the end of the shaft of the long bone adjacent to epiphyseal disc.

*Methemoglobinemia:* It occurs due to imbalance between oxidation and reduction of heme iron. When the heme iron is oxidized to ferric state, methemoglobin is formed.

*Microalbuminemia:* It is defined as period of incipient nephropathy with urinary albumin excretion rate (AER) of 20–200 µg/min or 30–300 mg/24 h. Microalbuminemia is related to duration of diabetes and is most common in postpubertal adolescents.

*Microangiopathic anemia:* This is mechanical hemolytic anemia in which red cell fragmentation is due to contact between red cells and abnormal intima of partly thrombosed, narrowed or necrotic small arteries.

*Microcytic:* The mean corpuscular volume is reduced, i.e., less than 76 fL and MCHC is within normal range, i.e., 30–35 g/dL.

**Miliary tuberculosis:** This usually occurs within a year of primary infection. The pulmonary form presents with temperature, dyspnea and cyanosis. In septicemic form, the child is delirious and disturbance of sensorium is seen.

**Milkmaid sign:** The child relaxes his grip off and on as if he is milking the cow. This is seen in Sydenham's chorea.

**Molluscum contagiosum:** It is caused by pox virus and characterized by well circumscribed dome-shaped tiny pearly papules or nodule up to 1 cm in size especially in intertriginous areas.

**Mongolian spots:** These are bluish well demarcated spots on the buttocks and trunk.

**Mongoloid facies:** It includes bossing of skull. Prominent frontal and parietal eminence with flattened vault, straight forehead, hypertrophy of maxilla. Prominent malar eminence, depressed nasal bridge and puffy eyes.

**Moon face:** It is characterized by a round face with prominent flushed cheeks and double chin seen in Cushing's syndrome.

**Moro's reflex:** The supine infant's hands are grasped and shoulders are lifted a few centimeters while keeping the back of the head on the bed. Then the hands are suddenly released. A positive response consists of sudden adduction of the arms at the shoulder and extension of the arm at the elbow. This is followed adduction of the arms and flexion of the forearm.

**Mulberry molar:** Abnormal first molar characterized by small surface and an excessive number of cusps. This is seen in congenital syphilis.

**Müllerian-inhibitory substance:** It is a glycoprotein hormone secreted by Sertoli cells of fetal testes. During sexual differentiation it causes involution of embryonic precursors of cervix, uterus and fallopian tubes.

**Myelodysplasia:** It describes various abnormal conditions of vertebral column that affects spinal cord function. These include meningocele and meningocele.

**Nadas criteria:** This criteria helps in assessment of the child for the presence or absence of heart disease. The criteria is divided into major and minor criteria. Presence of one major or two minor criteria are essential for indicating the presence of the heart disease.

**Neural tube defects:** These are the structural congenital anomalies. This implies the failure of

improper closure of neural tube and covering mesoderm and ectoderm.

**Neurofibromatosis:** It is autosomal dominant. It is characterized by cafe-au-lait spots, neurofibromas, freckling in axillary or inguinal region.

**Neutropenia:** It is defined as reduction in number of neutrophils below lower normal limit, i.e., 2500 cells/cu mm.

**Newborn/neonate:** Infant from birth to 4 weeks (28 days) is called a neonate or a new born. First week (7 days) of life is called early neonatal period. Late neonatal period extends from 7th to less 28th days.

**Nikolsky's sign:** Outer epidermis separates easily from basal layer on exertion of firm sliding manual pressure. This is seen with staphylococcal skin scalded syndrome (SSSS) and pemphigus.

**Nissen fundoplication:** This is curative surgical treatment of hiatus hernia. Here fundus of stomach is wrapped around lower 5 cm of esophagus.

**Non-Hodgkin's disease:** This is common among younger children. Clinical manifestations depend on anatomical site and extent of involvement. Systemic symptoms include malaise, anorexia and low grade fever. Chemotherapy and radiotherapy are mainstay of management.

**Nondisjunction:** These are the most common numeric chromosomal aberration. In metaphase of the first mitotic division, both members of the pair chromosome may move jointly during the anaphase to either of the daughter cells.

**Noonan syndrome:** The clinical features include broad forehead, hypertelorism, epicanthic folds, ptosis, low set ears, and webbing of neck. It is associated with cardiac disease, pulmonary stenosis and mental retardation.

**Normocytes:** Here mean corpuscular volume is within normal range, i.e., 76–97 fL.

**Olympian brow:** It is associated with recurrent periostosis and thickening of bone. This includes frontal bossing resulting in bony prominence of the forehead.

**Opsomyoclonus:** It is a paraneoplastic syndrome. The affected children have chaotic eye movements, myoclonus and ataxia. It is seen associated with neuroblastoma.

**Optic atrophy:** This is irreversible degeneration of the optic disc which disc becomes pale or white with the reduction in the number of capillaries

on the disc. There are two types, i.e., primary and secondary optic atrophy.

*Optic neuritis:* It is the inflammation of the optic nerve. If it is visible at the disc is called papillitis.

*Ortolani's maneuver:* The knees of the babies are flexed. The examiner places his thumb over inner aspect of thigh and his middle finger presses greater trochanter of femur. Baby's thigh is then adducted in dislocation of hip. The femoral head returns to acetabulum with a jerk.

*Osteopetrosis:* It is here do familial disorder in which partly calcified cartilagenous intercellular ground substance is not regularly reabsorbed and replace by regular osteoid tissue and bone.

*Otomycosis:* It is fungal otitis externa. It is most common in humid weather. There is pain and pruritis of the affected ear. Examination reveals fungal spores and filaments along with cloudy discharge.

*Oxytocin reflex:* Oxytocin is a hormone produced by the posterior pituitary. It is responsible for contraction of myoepithelial cells around the alveoli. This causes ejection of milk from the gland into the lactiferous sinuses and lactiferous ducts.

*Paget's disease:* It is an autosomal recessive disorder where serum levels of both calcium and phosphates are normal. Urinary leucine peptidase activity and serum acid phosphatase levels are increased. Bone turnover is reduced.

*Pagophagia:* It refers to a desire to ingest unusual substance such as ice or dust. This occurs in iron-deficiency anemia.

*Panarteritis nodosa:* It is a necrotizing vasculitis affecting small and medium sized arteries. Aneurysm and nodules may form at irregular intervals throughout affected arteria.

*Pancytopenia:* It occurs due to either failure of production of hematopoietic progenitors, their destruction or replacement of bone marrow by tumor or fibrosis.

*Papilledema:* It occurs as a result of increased intracranial tension. The optic nerve will have blurred disc margins and venous congestion. Disc is edematous and raised. Hemorrhages are evident with disc. The causes are increased intracranial tension, hypertension, *Guillain-Barré* syndrome, central retinal vein thrombosis, and pseudotumor cerebri.

*Patau syndrome:* It is characterized by severe developmental and physical retardation, microcephaly with sloping forehead and holoprosencephaly type of defect with varying degree of incomplete development of forebrain, olfactory and optic nerve.

*Pectus excavatum:* The lower port of the sternum appears depressed or funnel shaped. This may be a result of rickets or may follow chronic upper respiratory obstruction.

*Pel-Ebstein fever:* This type of fever is encountered in lymphoma. The fever is irregular and intermittent with febrile and afebrile states.

*Pemphigus:* It is a large flaccid bullae emerging on erythematous skin. It is commonly seen on face, trunk, pressure points, groin and axilla. Nikolsky's sign is positive. The disease is best treated initially with high dose of systemic corticosteroids. Azathioprine, cyclophosphamide, methotrexate and gold therapy have been useful.

*Pendred syndrome:* It is an autosomal recessive fashion. It is associated with congenital deafness and goiter. Hearing loss is usually presented at birth but goiter generally appears at puberty.

*Periodic breathing:* Respiration characterized regular cycles of respiration of 10-18 seconds interrupted by a pause of at least 3 seconds. The pattern recurs at least 3 seconds.

*Pertussis:* It is a highly contagious infectious disease of the respiratory tract caused by *Bordetella pertussis*. It is characterized by catarrhal phase, paroxysmal phase and convalescent phase. The triad of the disease is whoop, absolute lymphocytosis and decreased ESR.

*Phakomatoses:* These are nodular lesion, yellowish in color, refractile in nature or observed in tuberous sclerosis.

*Phimosis:* Normally seen up to the age of 2 years, the prepuce cannot be fully retracted because of congenital adhesions with the glands. In children, it may predispose to recurrent urinary tract infection.

*Pica:* It is an habit of eating nonedible substances such as clay, paint, earth, chalk, etc. These children usually have history of neonatal insults. There is no specific treatment.

*Pierre Robin syndrome:* It is a syndrome associated with micrognathia, occurring in association with cleft palate, glossoptosis and absent gag reflex.

**Pilonidal sinus:** It is a dimple located in midline intergluteal cleft at the level of the coccyx. It is seen relatively frequently in normal infants. An open sinus is a benign condition and is usually asymptomatic.

**Plantar fasciitis:** It is an inflammation of supporting structure of longitudinal arch owing to repetitive cycling. Pain increases with first step out of bed in morning. Treatment is by shin splints.

**Platybasia:** The first and second occipital segment and first and second cervical vertebra may be fused together. In this disorder medulla oblongata may get kinked over the odontoid process resulting in the compression of spinal cord tract and quadriplegia.

**Plumbism:** Toxic effects of lead are collectively known as plumbism. It involves many body system principally resulting in nervous, hematological and renal manifestation in children.

**Pneumatocele:** It is pathognomonic of staphylococcal pneumonia. These are progressively inflated abscess. These ultimately resolve and disappear within a period of few weeks.

**Poikilocytosis:** It is used to describe varied cell shape. Alterations include oval cells, pear and tear-shaped cells and sickle cells.

**Polyhydramnios:** This is a clinical condition wherein the amniotic fluid level will be more than 2000 mL. The associated anomalies include anencephaly, hydrops fetalis, ectopia vesicae, high intestinal obstruction and multiple pregnancy.

**Pompe disease:** Signs and symptoms of this disease result from lysosomal storage of glycogen in skeletal muscles, cardiac muscle and central nervous system. The heart is enlarged and appear globular. Death usually occurs before the age of 1 year.

**Port-wine stains:** These represent progressive ectasia of the superficial vascular plexus. These do not resolve spontaneously. These stains are typically pink in infancy. Face is commonly involved. This is best treated by 585 nm pulsed dye laser.

**Portal hypertension:** It is defined by elevation of portal venous pressure to values above 10–12 mm Hg.

**Potter's facies:** It is characterized by widely separated eyes, epicanthic fold, low set ear and broad nose. Chin is receding and limb abnormalities are seen. This is seen associated with infantile polycystic kidney.

**Prader-Willi syndrome:** Here both hypogonadotropic hypogonadism and hypergonadotropic hypergonadism occur secondary to cryptorchidism.

**Primary complex:** It is combination of draining lymphangitis and inflamed regional lymph nodes. This is seen in tuberculosis.

**Primary focus:** The inflamed area at the point of the entry of the tubercle bacilli is called primary focus.

**Proptosis:** Protrusion of the eye is called proptosis. It may be caused by shallowness of the orbit as in many craniofacial malformations. It may occur because of neoplastic vascular and inflammatory disorder.

**Puberty:** It is the period of life when the ability to reproduce sexually begins; characterized by maturation genital organs, development of secondary sexual characteristics and onset menstruation in females.

**Pulsus paradoxus:** Normally systolic blood pressure falls by 3–10 mm during inspiration. But in some conditions it falls below 10 mm, then pulse is called pulsus paradoxus. The causes include bronchial asthma, emphysema, cardiac tamponade and CCF.

**Rachitic rosary:** These are prominent costochondral junction seen in the rickets.

**Radial streak:** Pyelogram reveals opacification of dilated collecting ducts. Because these ducts extend from cortex to medulla, they appear as radial streak similar to spokes of a wheel. This is seen in polycystic kidney disease.

**Railroad calcification:** This is the type of calcification found in Sturge Weber syndrome. It is seen in occipital and temporal region on skull radiograph.

**Ramstedt's operation:** This is also called as pyloromyotomy. The hypertrophied circular muscle fibers are cut longitudinally completely without damaging the mucosa.

**Ranula:** They are the cystic lesions of the floor of the mouth. They are thought to be caused either by salivary gland obstruction or by salivary leakage from a traumatized sublingual and minor salivary gland.

**Red currant jelly:** It is typical description of the stool in intussusception. This occurs as a result of the inflammation of the bowel.

**Red reflex:** It is the red flare seen through the funduscopy through the pupil in normal infant.



**Reed-Sternberg cells:** These are the giant cells with multiple or multiloculated nuclei. It is the hallmark of Hodgkin's disease.

**Refsum disease:** It is due to the disturbances in phytonic acid metabolism. Clinical features include ataxia, ichthyosis and conduction defect in heart. These patients are treated by withholding green vegetables.

**Renal tubular acidosis:** It encompasses condition characterized by renal acidification. This result is hyperchloremic metabolic acidosis and inappropriately high urine pH.

**Retinal detachment:** This is the separation of the inner layers of retina from its pigment epithelium. In children, it usually occurs after the injury and will lead to the blindness if not detected and treated.

**Retinitis pigmentosa:** It is a bilateral disease resulting in blindness by middle age. Rods are mainly involved and night blindness is present. The disease may be primary or secondary to intrauterine infection or drugs.

**Reye's syndrome:** It follows confirmed adenovirus infection of several serotypes. It is characterized by bronchopneumonia, hepatitis, seizures and DIC.

**Rhabdomyosarcoma:** It is most common soft tissue sarcoma. It is one of the small round cell tumors. These are present with mass. The most common primary site is neck.

**Rheumatoid factor:** It is autoantibody present in rheumatoid arthritis. It acts as an antibody Fc fragment of immunoglobulin.

**Rickety rosary:** It is apparent costochondral junction seen in rickets.

**Riley-Day syndrome:** It is an autosomal recessive disorder involving peripheral nervous system. This is characterized pathologically by reduced number of nerve fibers that carry pain, temperature and taste sensation. There will be poor sucking and swallowing. Breath-holding spells are present.

**Risus sardonicus:** It occurs as a result of intractable spasm of the facial and buccal muscles in tetanus.

**Roseola infantum:** It is caused by human herpes virus. The onset is abrupt. High grade fever is associated with mild pharyngitis and coryza. Macular, maculopapular rashes appear and lasts for 24 hours.

**Sabre tibia:** It is anterior bowing of mid portion of the tibia. It is seen in congenital syphilis.

**Saddle nose:** It is depression of root of the nose. It occurs as a result of syphilitic rhinitis. It destroys adjacent bone and cartilage.

**Salmon patch:** These are the commonest vascular lesions in infancy. These are pale, pink to red macules seen over the glabella, upper eyelids or neck. Most fade by 1-2 years of age.

**Schaumann disease:** It is idiopathic kyphosis. This develops during adolescence. The cause is not known. There will be increased pressure on anterior vertebral growth plate.

**Scoliosis:** It is defined as lateral curvature of spine. The lateral curvature is always complicated by rotational deformity. It can be idiopathic, congenital, paralytic or postural.

**Scorbutic rosary:** This is prominent sharp and angular costochondral junction seen in scurvy.

**Sequestrum:** It is a piece of dead bone separated from normal bone. This is seen in osteomyelitis.

**Simian crease:** This refers to single palmar crease seen in Down's syndrome.

**Spur:** It is a projecting bone spike seen in scurvy.

**Staple sign:** It is subglottic narrowing seen in lateral chest radiograph. It is seen in croup.

**Status epilepticus:** It is characterized by repetitive prolonged seizures and patient remains unconscious in between the seizures or if the duration of the attack is more than 1 hour.

**Steatorrhea:** It is excess of fat found in stools of people with cystic fibrosis.

**Still's disease:** It is the systemic phase which precedes juvenile rheumatoid arthritis. It is characterized by hepatosplenomegaly and rashes.

**Stillbirth:** A fetal death (a product of conception that after separation from the mother does not any evidence of life) at gestation age 20 weeks or more or weighing more than 500 g.

**Strabismus:** It is deviation of eye which patient cannot overcome. It may be of paralytic or non-paralytic type. The visual axes of lens of the eye do not fall in parallel plane. This results in diplopia or a defective vision

**Stridor:** Abnormal produced due to narrowing/obstruction of larynx or trachea, mainly inspiratory in nature.

**Sunset sign:** It is downward deviation of the eyes so that each iris appears to set beneath the lower lid. This is commonly seen in hydrocephalus.

White sclera is exposed between sunset sign and upper eyelid. This is indicative of raised intracranial tension.

*Talipes:* It is characterized by plantar flexion and inversion of ankle. Dorsiflexion of the foot is limited. Corrective casts should be applied.

*Tay-Sachs disease:* It is autosomal recessive disease. Low serum beta hexosaminidase level is the characteristic metabolic defect. As a result GM<sub>2</sub> ganglioside accumulate in neurons. A cherry red spot is seen over the macular region or the retina. Death occurs by 2–4 years.

*Temper tantrum:* It is a kind of physical aggressive behavior. This happens when child cannot express his autonomy. The aggressive behavior may be in the form of biting, crying and throwing objects.

*Thermoneutral temperature:* The ideal environmental temperature for a new born at basal metabolic rate of the body is at minimum, oxygen utilization is least and maintains a core temperature between 36.5 and 37.5°C.

*Thrombocytopenia:* It refers to reduction in platelet count below 15000/cu mm. The causes include decreased production, sequestration of platelets in enlarged spleen.

*Todd paralysis:* It is paralysis or hemiparesis. It follows focal seizures. But weakness and neurological signs disappear completely within 24 hours.

*Tonic neck reflex:* The supine infants head is suddenly turned to one side. The arm and leg on the same side extend while the opposite limbs go into the flexion. The reflex is prominent in 2–4 months. Persistence of the reflex beyond 6–9 months indicate spastic cerebral palsy.

*TORCH:* It is a combination of infections like toxoplasmosis, rubella, cytomegalovirus and herpes simplex.

*Tracheomalacia:* It is a congenital anomaly associated with flabbiness of airway walls leading to collapse and airway obstruction. Tracheomalacia may be associated with bronchomalacia.

*Trendlenburg gait:* Here the glutei muscle on the affected side cannot keep the pelvis at level when the affected limb bears the weight so the pelvis is tilted to unaffected side. The level of the pelvis is checked by placing a hand on iliac crest.

*Trismus:* This condition occurs as a result of motor disturbance of trigeminal nerve. This is due to spasm of masticatory muscles which

result in difficulty in opening the mouth. This is one of the characteristic early symptoms of the tetanus.

*Trophic feeding:* This type of feeding is practiced in premature infants whose illness severity otherwise prevents advancement of enteral feeding volume. The purpose is to stimulate the GI tract functional and structural integrity.

*Turner's syndrome:* It is the most common monosomy. The finding is due to loss of the part or all of one of the sex chromosomes. The affected individual will have 45X. Phenotype is female and is characterized by short stature and underdeveloped gonad.

*Tzanck preparation:* This is useful in diagnosis of some viral infections such as herpes simplex, varicella, herpes zoster, etc. The base of the blister is scraped with blunt edged instrument. Staining with Giemsa stain is preferable. Balloon cells and multinucleated giant cells are characteristic of pemphigus.

*Vaso-occlusive crisis:* It consists of sudden attacks of bone pain, usually in limbs, joints, back and chest or of the abdominal pain. Infection is the precipitating factor.

*Vesicoureteric reflux:* It refers to the retrograde flow of urine from the bladder to the upper urinary tract. The rest in the intravesical pressure occurring during the micturition is freely transmitted to the ureter, renal pelvis, papillary collecting ducts and renal tubules.

*Von Gierke disease:* This is glycogen storage disorder. Clinical features include hepatomegaly, failure to thrive, hypoglycemia, ketosis and acidosis.

*Von Hippel-Lindau disease:* In this disorder, there are retinal, and cerebellar hemangioblastomas besides the spinal cord angiomas and cystic tumors of pancreas, kidneys, and epididymis. Patients show nystagmus, ataxia and signs of increased intracranial pressure.

*Von Willebrand disease:* It is autosomal dominant disorder and it occurs due to the deficiency of von Willebrand factor. Child presents with mucosal bleeding.

*Wegener's granuloma:* It is the vasculitis affecting upper and lower respiratory tract and kidneys. It is characterized by necrotizing granuloma. There will be nonspecific complaints. Ophthalmic involvement includes uveitis and orbital pseudotumor.

*Wheeze:* Abnormal high pitched musical sound produced due to the narrowing/obstruction of terminal airways, i.e., bronchi, mainly expiratory in nature.

*White reflex:* Absence of red flare when seen through the pupil with help of fundoscope. It is seen in retinoblastoma.

*Wimberger sign:* It is seen in scurvy, epiphyseal centers of ossification surrounded by the white ring is called Wimberger sign.

*Wiskott Aldrich syndrome:* It is an X-linked recessive disorder characterized by eczema,

thrombocytopenia and recurrent infections. There is profound IgM deficiency in addition to defective T cell.

*Xerophthalmia:* This occurs because of deficiency of vitamin A in diet. There is pigmentation of the cornea with the loss of normal luster and moist appearance of palpebral conjunctiva, which appears dry and wrinkled.

*Zoonosis:* An infectious that can transmitted from vertebrate animals to human beings. Common animals associated with zoonosis include cattle, dogs, cats, pigs, rats, and monkeys.

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